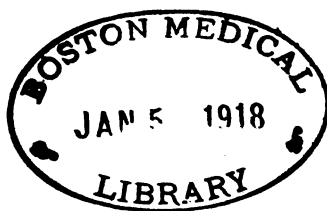
THE ACTIONS of DRUGS

A COURSE OF ELEMENTARY LECTURES
FOR STUDENTS OF PHARMACY

BY

TORALD SOLLMANN, M. D.
Professor of Pharmacology and Materia Medica
in the School of Medicine of Western Reserve
University, Cleveland

PHILADELPHIA AND LONDON
W. B. SAUNDERS COMPANY
1917

PREFACE

These lectures were delivered for several years to the senior students of the Cleveland School of Pharmacy. They were planned with the intention of giving to the young pharmacist a concise survey of the modern conceptions and knowledge of drug action. It was aimed to make this course "sound," but elementary; demanding but little previous knowledge of physiology or anatomy; and not pretending to fit the pharmacist for the treatment of disease. Obscuring details are intentionally omitted. The interested student should seek these, as needed, in larger works. I have endeavored to make the language non-technical; but the beginner may need a small medical dictionary.

T. S.

Cleveland, Ohio,
October, 1917.

CONTENTS

THE ACTIONS OF DRUGS

INTRODUCTION

Scope of the Lectures.—The following lectures will treat of the medical subjects a knowledge of which is essential to the professional pharmacist. This means a knowledge of the medical actions, uses and doses of drugs; and of the symptoms and treatment of poisoning.

We are confronted at the outset with the question of how much it is necessary or profitable for the pharmacist to know in this direction. In the medical schools, over 200 hours are devoted to these topics. The medical student, in order that he may understand these subjects thoroughly, must have pursued studies in anatomy, physiology and pathology for nearly two years; and before being able to apply the knowledge, the student is required to spend another two years or more in the study of disease.

This long study is considered by all those capable of judging as absolutely essential to the safety of the public. Any one who undertakes to treat disease with a lesser course of preparation faces serious legal complications, and even more grave moral responsibilities.

Limitations.—It would therefore be out of the question to give to students of pharmacy a course that would enable them to treat any kind of sickness. Indeed, it would be far better for the public, and even for the pharmacist himself, that the pharmacist should be entirely ignorant of medical actions, than that he should become possessed of the dangerous conceit that he is competent to advise or prescribe any treatment.

Value to Pharmacists.—Nevertheless, to the sensible and tactful pharmacist, some knowledge of these matters is very useful, and indeed necessary. As a tradesman, the public expects him to be familiar with the uses to which his wares are commonly put, and with the manner of their use. As a professional man, he can coöperate with the prescribing physician much better, if he has an intelligent understanding of the broad principles which guide treatment, of the objects which are to be accomplished and of the means that are utilized. The pharmacist himself will be protected against many blunders in the exercise of his higher professional function, the compounding of prescriptions. He will be able to protect the public against the errors of others, as well as his own. He may, by the exercise of some tact, put the physician under lasting obligations. In cases of poisoning, he has often the opportunity to institute preliminary treatment which may decide the patient's life.

It is, then, the object of these lectures to give the information that is useful to the pharmacist, without burdening and endangering him with other matters.

LOCAL AND SYSTEMIC ACTIONS

Some drugs act on the body at any place where they may be applied—the skin, a wound, the mouth, stomach, etc. Such actions are called *local.*

Other drugs affect only particular parts of the body; such as the brain, or muscles, or heart. To reach these, the drug must usually be absorbed, first of all, into the system. Hence, such actions are called *systemic.* The systemic effects are of course largely independent of the place of administration. Since there are so many parts of the body, and since each of these may be affected in several ways, the systemic actions are greatly diversified.

The local effects, on the other hand, depend almost entirely upon the place of application. Otherwise, they are relatively simple and uniform, and they therefore will serve to start us on our subject.

RUBEFACIENTS

Most local actions, in fact, resemble closely the results of mechanical injuries, especially those caused by excessive heat. The effects are due partly to the direct destruction of the body structure, and partly to the efforts of nature to repair this damage. This process of repair is what is meant by the word "*inflammation;*" and substances which produce local inflammation are called "*irritants.*"

These processes are best illustrated by what occurs in the skin when it is exposed to excessive heat. At first, there is more blood thrown into the part, which thereby becomes reddened, the condition returning to normal more or less quickly. Drugs used for this purpose are called *rubefacients.*

Alcohol.—This is one of the most useful rubefacients. It is applied on compresses (15 per cent.) or by friction (50 per cent.). The latter is more efficient.

Alcohol is also the main active ingredient of aq. hamamelidis, tr. arnica, sp. frumenti, sp. camphor, lin. saponis, etc. Some of these contain other ingredients, to be noted presently, which enhance the action and may raise it into the severer grades to be described.

Uses of Rubefacients.—The increased blood supply caused by these agents favors the processes of repair and healing; for these depend upon an active blood supply. They are therefore used in bruises, sprains, etc. They would not do so well for open wounds, for one thing because they would be painful.

Counterirritation.—Through the intact skin this sensory irritation results merely in smarting. This smarting is useful for relieving existing pains of certain kinds, such as rheumatism, lumbago, neuralgia, headache, toothache, etc. Such use of an artificial irritation to relieve pain or other irritation is called *Counterirritation.* It acts presumably by distracting attention, just as does the time-honored method of biting a bullet. This is the main use of the so-called *liniments,* which are only oily or soapy solutions of irritants.

The counterirritation may also have another purpose; namely, by dilating the blood-vessels of the skin, it relieves excessive blood supply or congestion of inflamed internal organs; for instance, in pleurisy, pneumonia, Bright's disease, etc. This is also called *revulsant action.* This effect, however, is now more commonly secured by the application of heat, in the form of poultices, or a simple hot-water bag.

Poultices.—Poultices, or cataplasmas, serve mainly this purpose of applying heat, and thereby dilating the cutaneous blood-vessels; though the maceration or softening of the skin is sometimes desirable, for instance for "maturing" boils. Physicians use them much less than formerly, because they frequently encourage infection; but they are still popular with the laity.

Linseed Poultice, or Cataplasma Lini.—This is prepared by stirring 1 cup of flaxseed into 2½ cups of boiling water. The latter may contain a pinch of sodium bicarbonate.

In the use of flaxseed, both the oil and gum play a part, in retaining the heat. The gum in particular takes up and retains the boiling water, and prevents excessive maceration of the skin. The linoleic acid of the oil is somewhat irritant, adding to the rubefaction. With a tender skin, this may be objectionable; hence the

addition of bicarbonate. The CO_2 liberated in the reaction makes the poultice lighter, more fluffy, and helps to retain heat.

Other Poultices.—To avoid the irritation, poultices may also be made, along similar lines, from purely starchy or mucilaginous substances—starch, flour, bread, slippery elm, etc.

Any of these poultices may be sprinkled or mixed with powdered charcoal, for the absorption of odors; or with mustard, to render it more irritant.

Mustard Poultice.—The typical mustard poultice is prepared by adding *tepid* water to a mixture of powdered mustard with 1 to 4 parts of flour, to make a thick paste. The water must not be warmer than tepid, because hot water destroys the ferment, which is required to form the volatile oil of mustard.

All other poultices must be *boiling* hot, and spread on sufficiently thick, one or two inches, to retain their heat.

Clay Poultice.—Clay or kaolin has been used as a poultice material since ancient times. Its use has been revived by the advertising of a proprietary poultice mass. It accomplishes nothing more or less than the linseed poultice—the conveyance of heat. Theoretically, it has the advantage that it is aseptic; and in the official cataplasma kaolini (N.F.) the attempt is even made—not very successfully—to render it antiseptic by the addition of a little boric acid and aromatic oils; while the glycerin renders it a little more rubefacient. The advantage of asepsis is rather illusory, for poultices should never be used in situations where they can carry sepsis. On the other hand, the heavy weight of the clay is a very real disadvantage. The clay poultice could well be spared.

Liniments.—These are liquid preparations of counter-irritants, dissolved in an oily fluid, or in "soap liniment,"

to secure their adherence to the skin, and to facilitate friction. The rubbing has often an important part in their effects. The official liniments give a good idea of the substances and proportions employed. Liniments are employed in rheumatic pains, sprains and bruises swellings, etc. *Soap liniment* consists of rosemary oil, camphor and alcohol, which act as rubefacients; and soap, which serves as a lubricant.

Sea-salt Baths.—These furnish an extensive but very mild stimulation, without injuring the skin. They are used as general tonics, similar to plain baths, but slightly more powerful. There is no special advantage in sea-salt; rock salt or common salt would be quite as good.

VOLATILE OILS

Use as Rubefacients.—All volatile oils are irritant, producing rubefaction, and rather deep sensory irritation, with little or no injury to the skin. They are, therefore, used often as ingredients of liniments. *Turpentine oil* is typical of the others. *Rosemary, thyme, cedar, sassafras,* etc. are also used. Their cost is higher, with no real advantage. *Camphor* and *menthol* may be counted in the same class. *Camphorated oil* (camphor liniment) is used against very mild pains, in bronchitis, etc. Menthol is especially used against neuralgia and headaches.

Internal Use of Volatile Oils.—When taken internally, these irritate or stimulate the lining of the air passages and digestive tract. The stimulation is used, for instance, in chronic bronchitis or cough, to "dry up" mucus. *Cubeba,* with the chemical derivatives of turpentine, *terpin* and *terebene,* are especially used for this purpose as "expectorants."[1] In the stomach, they act

[1] Expectorants: Drugs which act favorably on expectoration or cough.

as *carminatives*, that is, they cause expulsion of gas, and thus relieve "colic."

Peppermint is used in this way, and also other pungent substances, such as *ginger*, *chloroform*, *alcohol*, *asafetida*, etc.

Internal Uses of Turpentine Oil.—Volatile oils also expel gas from the intestine in "meteorism," or "tympanites," such as occurs in typhoid fever and after operations. For this, *turpentine oil* is used as "stupes" or enema. "*Stupes*" are cloths wrung out of hot water, sprinkled with turpentine and applied to the skin of the abdomen. For enema, the emulsion is used. *Turpentine* is also sometimes employed to expel tapeworms, but it is inferior to *aspidium* or *pelletierin*. Another use of turpentine is against phosphorus-poisoning. For this, old oil, so-called "ozonized," is preferred, since this oxidizes phosphorus.

Toxic Effects of Volatile Oils.—These consist mainly in irritation of the alimentary canal—diarrhea, often bloody; collapse; abortion; convulsive and paralyzing central effects. The treatment consists in evacuation (emetic and cathartic) and administration of mucilaginous substances.

Camphor.—This is used *externally* as a mild rubefacient, for "colds" and slight pain, etc. It may be employed as the camphorated oil, or spirit. Camphor is also a rather feeble antiseptic, often added to mouth washes.

Internally, camphor is a sort of popular cure-all. As used by the laity, its effects are probably imaginary. Its chief modern use in medical practice is as a stimulant for improving the pulse in acute cardiac weakness, fevers, etc. It is used hypodermically—1 c.c. of a 10 per cent. solution in sterilized oil.

Toxicology.—Overdoses of camphor cause convulsions and paralysis. However, the toxic dose and the effects

generally vary a great deal. When camphor spirit is taken, the actions of the alcohol generally predominate. The treatment consists in emptying the stomach by emetics and washing.

Menthol.—This is rather closely related to camphor, but produces a cool sensation in the skin. It is used mainly in headache and neuralgias.

Thymol.—This is another similar substance, but more actively antiseptic. It is used in mouth washes; and more recently, in larger doses, against hookworm disease.

Rubefacients in Toothache.—Creosote, aconite, cinnamon, cloves and capsicum are used to relieve this, all acting by counterirritation, *i.e.*, by producing a powerful but less painful sensory irritation.

Mustard.—The active volatile oil does not preëxist in the mustard seed, but is developed by the ferment in the presence of water. For this reason, mustard must be stored dry. Boiling destroys the ferment; hence, mustard poultices, etc., must be made up with lukewarm water, never with boiling water.

Mustard irritates more powerfully than ordinary rubefacients—the irritation may even progress to blistering or vesication, according to the length of application. The action, indeed, increases somewhat after the mustard is removed; it should therefore be applied only until tingling is felt. It is used *externally* ("sinapism"), as a poultice, plaster, baths—foot and general—and as an alcoholic or oily solution of the oil (2 per cent.). *Internally*, it produces a similar irritation; acting as a condiment or emetic, according to the dose.

Iodine.—This acts deeply, even to destruction of the skin (by caustic action); but the effect is easily controlled by the amount applied. It is supposed to be especially effective in promoting the absorption of swellings and effusions, as in dropsies, pleurisy, etc. The tincture

(which mixes with water, since it contains KI) is now used extensively in surgery to sterilize the skin before operation. The brown stain is easily removed by sodium thiosulphate or ammonia.

The natural resins, oleoresins and balsams may be considered in this connection. They are secretions of plants, the resins being insoluble in water, but soluble in alcohol and certain fat-solvents; the natural oleoresins are mixtures of resins and volatile oils; the balsams are similar mixtures containing cinnamic or benzoic acid.

Balsams (Peru, Benzoin, Styrax, etc.).—The aromatic acids confer distinct antiseptic properties and stimulate healing. They are therefore used as "vulneraries," *i.e.*, as applications to open wounds and especially slowly healing ulcers. The resinous character also serves to exclude air and infection. The *balsam of Peru* is used as such, or mixed with ointment. The *compound tincture of benzoin* (Turlington or Friar's balsam) serves similar purposes. The balsams have also a healing action on inflamed mucous membranes, and are used in bronchitis; either as the *syrup of Tolu*, or by inhaling the compound benzoin tincture with steam.

The Natural Oleoresins.—*Copaiba* is the principal representative of these. It is excreted by the urine, and is employed mainly for its action on the urethra in specific (gonorrheal) urethritis. The resin in the urine is precipitated by acids,[1] and may thus be mistaken for albumen. The distinction may be made by adding some alcohol or ether, which clear the copaiba precipitate. Copaiba causes more or less gastric irritation.

Rosin.—This exemplifies the resins. It is the residue left after distilling the volatile oil from natural turpen-

[1]The termination *itis* appended to the Latin or Greek name of an organ, signifies inflammation of that organ (urethritis, appendicitis, nephritis, etc.).

tine. Being solid, non-volatile, and insoluble in water, it is practically inactive, though very slightly irritant. It is utilized to give solidity to ointments and plasters.

Plasters.—These are used for local irritation; to convey medicaments; and for mechanical support. The local effect is due partly to the resin and to added ingredients (*capsicum, cantharides,* etc.), partly to the retention of the secretions of the skin, resulting in maceration. Where this is undesirable, it may be partly avoided by making the plaster "porous." The use of plasters for the conveyance of systemic medicines is now largely abandoned, the absorption being too uncertain. Their principal use is mechanical, in surgery. In this, rubber has largely taken the place of the older ingredients.

VESICANTS

Mechanism of Action.—Recurring to the familiar example of cutaneous irritation by heat: if the severity of a burn exceeds the degree of rubefaction, blisters or vesicles are formed; hence the term "**vesication.**" This is likewise the next degree of the action of irritant drugs, and those drugs which are practically used for this purpose are called vesicants, or *epispastics* (meaning to "draw after").

In order to understand the mechanism of their action, we must premise some anatomical and physiological details:

Anatomy of the Skin.—The skin contains three principal layers:

1. *Stratum Corneum.*—This consists of flat horny cells, impermeable to water; as we proceed deeper, these become thicker and softer, and pass into the:

2. *Stratum Mucosum.*—Soft cells, permeable, similar to those of the mouth. Beneath these are the:

3. *Papillæ.*—These consist of fibrous tissue, bearing blood-vessels, lymph-vessels and nerves.

Constituents of the Blood.—The blood consists of a suspension of small cells (corpuscles, red and white), in a nearly colorless fluid (plasma). The *red corpuscles* (erythrocytes) are by far the more numerous. In mammals they consist of small, circular button-like discs, tinged amber by the blood pigment (hemoglobin); in frogs and birds they are elliptical and have nuclei. In man, they have a diameter of 8 mcm. (micromillimeters) and number 5,000,000 to the cubic millimeter. They make up about one-third the volume of the blood. Their number is decreased in the various anemias, and their shape and hemoglobin content may also be altered. Their function is the conveyance of oxygen to the tissues, the element being carried in loose combination with the hemoglobin.

The *white corpuscles* (or leukocytes) are much less numerous (about 1:500 of red). They are derived from the lymph, spleen and other tissues. They execute ameboid movements, by which they can engulf bacteria; and they are otherwise concerned in the protection of the body against infection. Leukocytes, living and dead and degenerated, constitute the main formed elements of *pus.*

The *plasma,* the liquid part of the blood, is a watery solution containing 8 or 9 per cent. of proteins, mainly albumin and globulin; 0.6 per cent. of sodium chloride; and traces of sulphates, phosphates, carbonates, calcium, and other salts; having a slightly alkaline reaction to litmus paper. It serves to carry nutriment to the tissues.

Coagulation.—When blood is shed from the body, it undergoes a peculiar change: in a few minutes it loses its fluidity, and sets into a compact jelly or clot. This is due to the conversion of a dissolved protein, fibrinogen,

into a fibrous substance, fibrin. The transformation is effected by a ferment, and requires the presence of calcium salts.

The amount of fibrin is quite small, about 1/3 per cent.; but it forms a fine network which enmeshes the corpuscles and the liquid, so that the entire blood appears solidified. In time, the fibers gradually contract, and squeeze out the liquid, which is now called *serum*. Serum differs from plasma in that it does not coagulate, the fibrin being already separated.

Filtration of Blood and Lymph.—The blood circulates through the body in a closed system of tubes, the *blood-vessels*. The walls of the blood-vessels become progressively thinner as they pass from the heart to the periphery, until, in the smallest vessels or capillaries, they consist of a single layer of extremely thin cells (endothelium).

In no place, however, does the blood come into direct contact with the tissue cells, which it has to nourish. This contact is brought about by another fluid, the *lymph*, which fills all the interstices between tissues, and thus bathes all the cells. The lymph may be considered as mainly a filtrate from the blood. The plasma and some of the white corpuscles are being constantly filtered through the capillaries into the tissue spaces, and constitute the lymph. The lymph gradually finds its way into larger vessels, and finally back into the large veins. There is thus a constant stream of lymph.

The filtration of lymph is greatly increased when inflammation sets in. If inflammation is intense, more lymph is filtered than can be carried off by the lymph-vessels. This accumulates in the tissue spaces and takes the path of least resistance; in the mucous membranes, this is toward the surface. In the skin, it cannot reach the surface because of the impermeable horny cells which

occur between the stratum corneum and mucosum. The lymph therefore accumulates and produces a blister or vesicle.

Cantharides.—This is the principal vesicant. Its active constituent is a neutral principle, *cantharidin.* It is generally applied as a cerate, which, when spread, constitutes a cantharides plaster. As this is not adhesive, it is best held in place by strips of adhesive plaster. It is left applied for several hours, until a blister of the required size is raised. "Flying blisters" are a succession of small blisters, raised by the application for a short time to successive areas. Short application may be used for rubefaction, and sometimes a liniment is made more rubefacient by the addition of tr. cantharides. Similarly, dilute solutions are also employed in baldness.

Vesicants proper are used when a powerful counter-irritation is desired. Cantharides should be employed only under the advice of a physician, since its use may involve some danger. Cantharidin is rather readily absorbed from the skin, and may then produce inflammation of the genito-urinary tract and kidneys, especially if they are already inflamed. It is now rarely if ever administered internally.

Other Vesicants.—If blisters are necessary in patients with kidney inflammation (Bright's disease, nephritis), it may be necessary to use one of the other vesicants—chloroform or strong ammonia or iodine—but these are not as efficient or convenient as cantharides. Other rubefacients are also vesicant on sensitive skins.

Poison Ivy.—Several species of Rhus produce inflammation of the skin (dermatitis) ending in vesication. They are not used therapeutically, but are of toxicologic interest. The active principle has the physical characteristics of a fixed oil or resin. This suggests the proper treatment. This should be carried out as soon as pos-

sible after infection (if possible before inflammation has started) by thorough scrubbing with soap to remove the oil. A saturated solution of lead acetate is a time-honored remedy, especially after the dermatitis has set in. It acts partly as an astringent, and partly by precipitating and perhaps destroying the oil. Other metallic salts act similarly, but perhaps not quite as efficiently. Grindelia, and the juice of *Impatiens*, are also employed. Salves should *never* be used, as they only spread the infection. Certain other plants also produce dermatitis in susceptible individuals, *e.g.*, *Primula*.

PUSTULANTS

Certain irritants lead to the production of pus. Since they pass more easily through the openings of the glands, and therefore are more concentrated here, the pus formation occurs especially at these openings. This is termed pustulation. The local application of *antimony* (tartar emetic) and *croton oil* are examples. The irritation is more severe and especially more lasting than with other irritants. They are now rarely used.

CAUSTICS

Strong heat kills the cells of the skin and underlying tissues; and extreme heat causes their destruction or chemical disorganization. This is the equivalent of "caustic" action. A very violent irritation may kill the cells; but the caustics also enter into direct chemical combination with the cell-proteins and thus cause their destruction. To this class belong acids and alkalies; free bromine, chlorine and iodine, and certain metallic salts and oxides, particularly of mercury, silver, arsenic and chromium.

The effects differ somewhat according to whether the

compounds formed by the caustic and the tissues are fluid or solid, soluble or insoluble.

Alkalies.—The *alkalies*, for instance, actually dissolve the tissues. Hence, their action spreads deep and wide, and is so difficult to control in its severer grades that alkaliés are practically unmanageable as caustics. The mildest degree of this alkali action is used, however, in the employment of *soap* and *borax* for softening the skin and removing the superficial squames of epidermis, and in the employment of *sodium bicarbonate* and borate for thinning catarrhal mucus. A somewhat stronger degree of this action is employed for the softening and removal of hair. The *alkaline sulphides* (for instance, calcium sulphide) are especially used as "*depilatories*" (*de*, off; *pilum*, hair). Their use is not advisable, since it is apt to injure the skin, especially if they are employed continuously.

Calcium sulphide is sometimes used internally against boils. This has no rational foundation.

The Halogens.—Bromine and iodine also penetrate too diffusively and too deeply to be available as cauterizants.

The Acids and the Metallic Salts.—These, on the other hand, tend to form insoluble compounds with the tissue elements. This retards their penetration, so that the depth of their action can be fairly well controlled. In its mildest grades, this precipitation of the proteins leads to the phenomena of astringent action, which will be described later.

The practical value of silver nitrate is very largely due to the ease with which its action can be graded, from slight astringency to deep corrosion.

The precipitated or coagulated proteins form a solid mass over the corroded area—the *scab* or *eschar;* hence these corrosives are also called *escharotics*.

Uses of Caustics.—Caustics are sometimes, but rarely, used to produce severe counterirritation. More commonly they serve for the removal of *abnormal tissue growths*—warts, polypi, cancer, etc. Their use against cancer is not to be advised, since they generally fail to destroy it completely, in which case it is apt to recur with greater virulence. It will then be too late to adopt operative procedures.

When swallowed, the caustics produce very violent symptoms, which will be discussed presently.

EMOLLIENTS AND DEMULCENTS

Irritation or inflammation, as we have seen, is a departure from normal, a pathological condition, or disease. As such, it may be induced intentionally for correcting other diseased conditions; on the other hand, it may itself require treatment. This may be accomplished in some cases, particularly those of long standing, by modifying the type of inflammation through a special class of irritants, called astringents, which we will consider presently. In acute cases the treatment consists in protection by fatty, oily or gummy substances.

These, by forming a difficultly permeable covering or pellicle over the inflamed surface, tend to exclude external irritants. The same object may be accomplished by the use of indifferent *dusting powders,* such as *talcum, lycopodium,* and the *basic bismuth salts.* The latter, however, also have antiseptic, astringent and stimulant properties.

The character of the protective substances must vary somewhat, according to whether they are to be applied to the skin or to mucous surfaces. The skin requires fluids which do not dry readily, such as the oils, fats and unguents. Since these also soften the skin, they are called

emollients (to soften). Internally this is not so essential, and the gummy substances are more suitable, since they adhere better to the moist mucous surfaces. These are called *demulcents* (to smooth). It is interesting to observe that these correspond to the natural protective secretions of the body—the skin being covered by a thin layer of oily secretion, and the mucous membranes by the mucous secretion, which is closely allied to the gums. Glycerine partakes of the character of both types.

GENERAL TOXICOLOGY

We have thus far considered irritants as therapeutic agents. When properly used they do much good. Used improperly, they do much harm and act as poisons. This phase of the subject is of great importance; but before entering upon it, it is well to consider some of the general data of toxicology, the science of poisons.

Definition of Poison.—What is a poison? The popular conception does not quite agree with the scientific; and in law, again, there are various definitions. The differences concern mainly a few relatively unusual agents. Ordinarily, one may therefore be fairly well satisfied with the definition that "a poison is a substance which may cause poisoning."

A poison (from potion, a draught), by the broadest definition, is a substance the administration of which is injurious to health. However, injurious mechanical, physical, or bacterial agencies are not commonly classed as poisons; nor are the substances which produce injurious effects only in very large doses (say over 50 Gm.). It is very difficult to give a definition which will not be ambiguous in some cases. The following covers most of the points which must be considered in classing a substance as a poison:

A poison is any substance which, acting directly through its inherent chemic properties, and by its ordinary action, is capable of destroying life, or of seriously endangering health, when it is applied to the body, externally, or in moderate doses (to 50 Gm.) internally.

Restriction of Sale of Poisons.—Poisons have legitimate functions in the arts and in medicine; but it is one of the functions of government to restrict their sale so as to protect the public against their abuse for mischievous ends. This is accomplished universally by restricting the right to their sale to responsible and discriminating persons; and as such the pharmacists have been practically exclusively selected. The right to sell poison is the most conspicuous difference between the pharmacist and an ordinary tradesman; so that it becomes an external badge of his professional character. A very high compliment is thus paid to the integrity and intelligence of the pharmaceutical profession. In return, the pharmacist should be ever mindful not to forfeit in any way the confidence which is thus placed in him. To this end, he should carefully study the Poison Acts, Federal and State, and observe in detail, in the spirit as well as in the letter, the special rules and restrictions which the law places about the sale of poisons, for his own protection as well as for the safety of the public.

Etiology of Poisoning.—Poisoning may result through criminal or suicidal intent, or through accident.

The statistics of the relative frequency of the different forms of poisoning vary from year to year, and with each country. A classified list of deaths from poisoning in the U. S. registration area is given by Wilbert, 1916. Suicidal poisoning is probably the most frequent, nearly a half of the suicides in the United States being due to poisoning.

It is calculated that here five-sixths of all suicidal cases are due to phenol. There is, however, a fashion in poisons, as in other things. This is greatly fostered by the notoriety which the newspapers often give to these cases.

Administration and Absorption of Poisons.—Poisons may reach the body through any part of its surfaces, external or internal. This modifies, in the first place, their local effects. It also modifies somewhat their

remote or systemic effects, by influencing the rate of their absorption. This is of equal importance in the medicinal use of drugs.

Factors Influencing Absorption.—Absorption is modified, in the first place, by the physical state of the drug, particularly by its solubility and diffusibility. Other things being equal, the more soluble a drug, the more easily it is absorbed. Insoluble drugs, however, are often brought into solution by chemical changes in the alimentary canal. Thus, oils are rendered soluble by saponification; esters, like phenyl-salicylate, are split into their components; both these effects are accomplished by the lipolytic ferment (steapsin) of the pancreatic juice. Insoluble metallic salts or oxides are converted into soluble chlorides by the acid of the gastric juice; these combine with the proteins, thus preserving them from precipitation in the alkaline intestine, etc. It is therefore not possible to predict that a substance which is insoluble in water will also be insoluble in the body.

Absorption from Digestive Tract.—In the alimentary canal, the mouth is a relatively good absorbing surface. The stomach absorbs very little. The main absorption occurs in the intestine. The rapidity of absorption, and therefore the rapidity of action, depends very largely upon the rapidity with which the drug passes through the stomach into the intestine. This, again, depends upon the state of digestion. When the stomach is empty, a drug in solution passes through it almost instantly; whereas, after a full meal, it may remain for a couple of hours. Hence a poison is much less dangerous when it is taken after a full meal. On the other hand, when one wishes to obtain a rapid and full medicinal effect, the medicine should be given on an empty stomach, *i.e.*, at least two hours after a meal—unless it is necessary to avoid gastric irritation.

Influence of Extractives.—The presence of food, gum, and extractives also delays absorption. Hence galenic preparations act more slowly, even on hypodermic administration, than, for instance, the pure alkaloids.

Hypodermic Injection.—With hypodermic administration, absorption is very rapid, if the drug is soluble. This makes the dosage more certain, and somewhat smaller doses suffice. It is especially indicated when a very quick action is essential. It cannot be used with irritant drugs, however, on account of pain and abscess formation. The intramuscular injection is even more effective, and less irritant.

The Rectum.—This is a good absorbing surface, when the drug is given by enema; somewhat slower by suppository.

The Lungs.—The quickest absorbing surface is the lung; and the action of easily volatile substances (coal gas, hydrocyanic acid, nicotine, etc.) is almost instantaneous. Fortunately, the excretion is equally prompt, so that vigorous artificial respiration, if started in time, may save the patient.

The Skin.—The intact skin is practically impermeable for watery solutions; but somewhat absorbent for oily solutions; especially for solutions in true fats or oleic acid. The ointments made up with petrolatum are better suited for strictly local superficial effects.

The broken skin, open wounds and ulcers, absorb easily, similarly to hypodermic injections.

The Recognition (Diagnosis) of Poisoning.—This is essential both to treatment and justice. During life, it is in the province of the physician; after death, in that of the analytic chemist; but the pharmacist, if he has the first access to the case, can render material assistance to both.

For criminal conviction it is necessary that the nature

of the particular poison be ascertained; but for treatment, the first question is whether any poison whatever has been used; and this often suffices, for the treatment of many poisons is very similar.

The particular symptoms (*i.e.*, the phenomena presented by the patient) often indicate, and sometimes prove, what special poison has been used. The pharmacist, therefore, should observe keenly whatever passes, and communicate his observations to the physician on his arrival.

Symptoms of Poisoning and Classification of Poisons.—*Suspicion of poisoning* is aroused if a person, previously in good health, manifests rather suddenly marked pathologic symptoms, which become rapidly worse. The suspicion becomes more firm, if the phenomena appear a short time after swallowing some substance which may perhaps have an unusual odor or taste;[1] if they agree in character with those produced by some group of poisons, and if they do not agree with any other disease.

Symptomatic Classification of Poisons.—The following classes are generally recognized:

1. **Irritants.**—These produce inflammation; if they are taken by the mouth, there is pain throughout the alimentary canal, vomiting, purging, delirium, coma. Most poisons are to some extent irritant, so that these symptoms are almost universally present. The irritants can be subdivided into *corrosives*, which produce a direct destruction of tissues; and *simple irritants*, which do not. If corrosives are taken by the stomach, the vomit is often bloody.

2. **Nerve Poisons.**—These act on the neuromuscular apparatus, and include most of the poisons which are fatal in minute doses. They are subdivided into: **Convulsants**, which cause spasms; **Som-**

[1] It may appear strange that poisons which possess a pronounced and disagreeable taste could be used for criminal poisoning, except with infants; but a moment's thought will show that if a liquid is taken unsuspectingly, the taste is not noticed until a large amount has been swallowed.

nifacients, causing sleep and coma; and **Cardiac poisons, which** stop the heart.

3. Blood Poisons.—Those which alter the hemoglobin or blood corpuscles. These include the toxic gases, the nitrites, etc. Their action is generally characterized by cyanosis.

It must not be supposed that the action of a poison is confined generally to one class of structures or functions. All functions suffer directly or indirectly, and whatever the class to which the poison belongs, the final **cause of death** is, in almost all cases, a paralysis of respiration, preceded by the phenomena of *asphyxia*. In virtue of the latter, or through other causes, the urine often contains sugar.

The irritants, and especially the corrosives, produce lesions which can be demonstrated at AUTOPSY. With other poisons the postmortem examination is generally negative. The SPECTRUM OF THE BLOOD shows characteristic changes with some poisons. These are also apt to cause ecchymotic discolorations of the skin. Antiseptic poisons *delay the putrefaction* of the body, so that mummification may result. Convulsive poisons quicken the onset of *rigor mortis*.

For the *detection of the poison*, and to aid in fixing the guilt on the proper person, the physician must carefully observe the symptoms, take possession of any suspected material, medicine, vomit, etc., and in case of autopsy, preserve the stomach and its contents, the intestines and contents, blood, liver, kidneys, and portions of other organs, *separately*, without antiseptics,[1] in clean, hermetically closed glass vessels, which should be sealed with wax.[2] An exact *written record* of all the observations should be made as soon as possible.

The *symptoms* in cases of suspected poisoning are very rarely sufficient to affirm the presence or nature of a poison, although they may be of great aid to the analyst.

[1] Even glucoside and alkaloid poisons can be isolated for a long time (160 to 270 days) from putrefying masses. Some poisons, however, disappear rapidly (phosphorus, cyanide, picrotoxin, phenol, etc.). Strychnine and morphine are very persistent.

[2] In emergency, a rare or specially marked coin, or a key, may serve to impress the seal.

The final proof rests generally on the results of the *chemic examination.*

So much depends on this analysis, that it should never be undertaken by any one who has not had extensive experience in this class of work, and who has not the necessary facilities. It lies outside of the scope of the ordinary pharmacist. The latter should, however, be familiar with the general outline of the process used for isolating poisons; and with such chemic tests as may be quickly applied. These tests are often valuable for diagnostic and therapeutic purposes.

Some poisons can be demonstrated much better by tests on animals than by any chemic tests. For this object, they should be isolated in as pure a form as possible.

Among the many precautions which must be employed, we may perhaps mention the errors apt to arise from embalming fluids, which often contain arsenic.

OUTLINE OF TOXICOLOGIC ANALYSIS[1]

Precautions.—The first duty of the analyst is to guard the material confided to him from *the wilful or accidental introduction of poisons.* For this purpose, precaution must be taken that no other person has access to the material; and every reagent and apparatus must be tested personally.

As a rule, the different organs must be kept strictly separated throughout the analysis. It will depend on circumstances whether the analysis of the individual organs is made at the same time, or successively. If the latter is decided on, the largest organ, or that most likely to contain the poison, is examined first. It may be advisable, however, to mix a weighed quantity (one-fourth or one-third) of the comminuted organs, and to use this mixture for the first analysis.

Since the material to be analyzed is usually limited in amount, and cannot be replaced, the examination must be arranged in such a way that as many tests as possible can be made successively on a single sample of the material. An economy of time and material is also secured by obtaining, as quickly as possible, some idea of what poisons may be present. This may be done by some easy

[1] Gadamer's "Lehrbuch der chemischen Toxicologie" is an excellent reference book.

preliminary tests, or by using so-called "group-reactions" which, if negative, will exclude a number of substances. The symptoms may also have furnished some important hints, but should not prevent the complete examination of the substance.

During the isolation and the preliminary search for the poison, only the most important tests should be applied. When the poison has been isolated, however, it should be subjected to every known test. A sample of the isolated poison should be preserved, in stable form.

Preliminary Examination.—The **systematic examination** is begun by a careful inspection of the portions of the alimentary canal. These are opened, and extended on an inverted evaporating dish, mucous surface upward. Pathologic lesions are looked for, as also particles of the poison which may be adherent. A magnifying lens should be employed. (Granules of arsenic have often been isolated in this way.) The contents of the alimentary canal, or vomited matter, are subjected to a similar close inspection. The odor should be carefully observed. During this examination, the **reaction to litmus paper** should be noted (caustic acids or alkalies).

Each organ is then hashed, carefully weighed, and replaced in hermetically sealed jars.[1]

Isolation of the Poison.—No routine schema of analysis will fit all cases, since each presents its own problems. However, the following illustrates the usual procedure.

Division of Material.—Ordinarily, each organ, after comminution, is divided into the following portions carefully weighed: One-third is reserved for control; one-twentieth for preliminary tests. The remainder is divided into four parts, used respectively for the search for volatile, fixed organic and inorganic poisons, and for reserve. If the quantity of material is very scanty, two equal portions will suffice: one is reserved for preliminary tests, easily decomposable poisons, and control; the other is examined succes-

[1] As soon as the absence of volatile poisons has been proven, the contents of the jars may be covered with 95 per cent. alcohol.

sively for easily volatile poisons, for fixed organic poisons, and for metals.

Volatile Poisons.—A portion of the material is acidulated with tartaric acid (adding water if necessary), and distilled from a flask or retort connected with a Liebig's condenser.[1] It is advisable to pass a slow current of live steam through the mass. The distillation is continued until about two-thirds of the liquid have been collected. The distillate is collected in three portions. The odor is noted (volatile oils, chloroform, ether, etc.), and the characteristic tests applied for phosphorus, phenol, cyanides, alcohol,[2] chloroform, chloral, etc.

Phosphorus.—A preliminary test for this element must be made with silver nitrate and lead acetate papers before the distillation is begun. If this test indicates its presence, the condenser is set vertically downward, and the distillation is carried on in a darkened room. All air is expelled from the apparatus by a stream of carbon dioxide. This is then shut off, and replaced by live steam, the flask being heated at the same time. If phosphorus is present, a luminous ring appears in the tubes or condenser, shifting its position when the heat applied to the flask is altered (*Mitscherlich's method*). The appearance of this phenomenon proves the presence of phosphorus absolutely.

There are, however, quite a number of substances the presence of which interferes with the formation of this ring. Almost any volatile substance may do so; turpentine, chloroform, ether, alcohol; and alcohol is often present, as it is usually given as an antidote.

The absence of the ring does not therefore prove the absence of phosphorus. The distillate will contain phosphorus in the lower stages of oxidation, as phosphorous or hypophosphorous acid. The best way to prove phosphorus in this is to add some bromine water to the distillate and to evaporate to dryness. This results in phosphoric acid, which may be demonstrated by magnesia mixture or ammonium molybdate. The quantitative determination of phos-

[1] See below for special arrangement to be used when phosphorus is present.

[2] Alcohol is only important if it is present in large amounts. Smaller quantities may be present accidentally or as antidote.

phorus is not important; because if it is present at all, it is present as a toxic agent.

Cyanides.—The presence of mere traces of hydrocyanic acid in the distillate is no proof of poisoning, since these may have been introduced in the way of food (almonds or other seeds). A *quantitative estimation*, by means of silver nitrate, may be necessary. The qualitative proof also requires two further precautions:

With the method which we have given, ferrocyanides might also be decomposed and give rise to hydrocyanic acid; and since ferrocyanides are not toxic, this would lead to wrong conclusions. To eliminate this, the original liquid is filtered and the Prussian blue test applied to it directly. Mercuric cyanide does not yield its hydrocyanic acid in this treatment. If it is suspected, the material must be treated with hydrogen sulphide.

Distillation from Alkaline Solution.—It is sometimes recommended to add water to the residue in the retort, to make it alkaline with sodium carbonate, and to distil again. The distillate contains ammonium, amines, chloroform (if chloral was present) and the volatile alkaloids. This step may generally be omitted, as these poisons are discovered in other parts of the process; or a small sample may be heated in a test-tube with sodium carbonate and the odor noted.

Extraction of Fixed Organic Poisons.—The extraction, separation and purification of these poisons are based on their special solubility in certain solvents. As a rule, they are fairly soluble in acidulated water and alcohol. The neutral principles are removed from the acid watery solution by ether or chloroform. The alkaloids are dissolved by these substances only after the addition of an alkali.

In brief outline, the suspected material is first extracted with boiling acidulated water and alcohol. The acid watery extract is then treated with ether, which dissolves *neutral principles* and various impurities, but which leaves the *alkaloids*. These are extracted later by fresh ether, after rendering the solution alkaline.

Various methods are in use. The most practical is that of **Stas-Otto**, slightly modified:

§1. The poisons are first *brought into solution* by boiling the material, if solid, with about 5 parts of water for fifteen minutes (or the residue remaining after the distillation of the acid solution may be used). The mixture is cooled and strained. This *removes fat, coagulable protein, fiber, etc.*[1]

§2. The strained solution is evaporated at a low temperature to a syrupy consistency, and boiled with twice its volume of alcohol, for fifteen minutes. The evaporated alcohol is replaced. It is then filtered, and the filter washed with alcohol. This *removes salts, non-coagulable proteins, etc.*

§3. The alcoholic filtrate is diluted with an equal volume of water and filtered. This *removes resins, fats, etc.* (The residue may be examined for cathartic resins and croton oil.) (For further purification, the filtrate may be again treated by §§2 and 3.)

§4. The filtrate, which should have an acid reaction, is now shaken in a separatory funnel with 10 c.c. of ether. This is drawn off, and the same process is repeated twice. The ether *removes neutral principles, picric acid, and salicylic acid.* It is filtered and allowed to evaporate in a glass capsule, and the residue is purified and tested for these acids, for caffeine, cantharidin, colchicine digitalin, picrotoxin, and the coal-tar antipyretics.

§5. The watery solution, remaining from the extraction with ether in the last paragraph, is now made fairly alkaline with sodium carbonate (*to liberate the alkaloids*) and again extracted with ether, as in the last paragraph. From this alkaline solution, the ether *removes all alkaloids except morphine.* The ethereal layer is filtered and evaporated, the residue is purified, and tested, first by potassium mercuric iodide, then for physostigmine, apomorphine, nicotine, coniine, veratrine, strychnine, brucine, atropine, cocaine, codeine, narcotine, emetine, and aconitine.

§6. *To isolate the morphine,* the watery liquid remaining in the last paragraph, is made acid, then alkaline by ammonia, and shaken at once with acetic ether, or with *hot* amyl alcohol.

§7. To test for *oxalic acid,* the original substance is partly dried, extracted with 5 c.c. of hydrochloric acid and 20 c.c. of boiling alcohol, for half an hour, filtered, evaporated, extracted with water, and tested by Ex. 10, No. 25. *Santonin* and *meconic acid* must also be extracted by special methods.

Dragendorff's Method.—In this, a more extensive separation of the poisons is obtained, by multiplying the solvents and operations.

[1] It is understood that the remaining mass should be washed, in every instance of filtration or straining.

The preliminary treatment is as per §§1, 2, and 3. The acid solution is then exhausted successively by petroleum ether, benzol and chloroform; and then in alkaline solution by the same sequence of solvents, and finally by amyl alcohol.

Kippenberger's Method.—This possesses the advantage of separating the poisons in purer form from the start, but it involves technical difficulties. It depends on the insolubility of the tannates of proteins in glycerine, while the organic poisons are soluble in this medium. The solid material (say 100 Gm.) is digested for two days at 40°C. with 10 Gm. tannin, 1 Gm. tartaric acid, and 100 Gm. glycerine. The mass is expressed, the residue is washed with tannic glycerine. The fluids are diluted with water, heated to 50°C. and filtered. The filtrate is then extracted twice with petroleum ether, which removes mainly fats. The glycerine layer is then extracted as in the Stas-Otto method (§§4 and 5), but using chloroform in place of ether.

For *the purification of the alkaloids*, the residue, left by the evaporation of the chloroform, is dissolved in acidulated water, neutralized, and at once precipitated by iodine-potassium-iodide. The precipitate is collected on a small filter, washed with cold water, dried, and dissolved in hot acetone. The filtered acetone solution is treated first with alkali, then with acid, then with water; the acetone is expelled on a water-bath, and the remaining watery solution is decolorized by sodium hyposulphite. The solution is then made alkaline with sodium carbonate and extracted with ether or chloroform.

Physiologic Tests.—The poisons isolated by these methods are often not sufficiently pure to give the typical chemic tests; furthermore, certain of the tests are closely simulated by ptomains. This holds true also of the physiologic tests, *i.e.*, the effects on animals. The only way to distinguish with certainty between these is to use both the chemic and the physiologic tests. For, as far as is known, there are no ptomains which give both the chemic and physiologic tests of one alkaloid.

The physiologic tests can generally be obtained with fairly impure preparations. They are most typical in the case of strychnine, atropine, physostigmine, aconite, digitalis group, picrotoxin, veratrine, cantharidin, croton oil. The subject is elaborated in Fuehner's "Nachweiss von Giften."

Isolation of Fixed Inorganic Poisons.—The residues of the preceding operations may be used for the search of

these poisons. The usual methods of inorganic analysis are followed; but it is superfluous to test for non-poisonous constituents.

The absence of many metallic poisons can be quickly shown by Reinsch's test. This does not, however, dispense from further tests. Only an outline can be given here:

A: Destruction of Organic Matter and Solution.—*Method of Fresenius and Babo.*—Organs or syrupy residue, plus 300 c.c. to 500 c.c. of arsenic free HCl (1 : 2) in liter flask: heat lukewarm. Add 4 to 6 Gm. $KClO_3$ in 0.5 Gm. portions, till dissolved. Evaporate to about 100 c.c. (no free Cl). Dilute to 400 c.c. Add 2 c.c. dilute H_2SO_4. Stand overnight. Filter. *Filtrate* = *B*. *Residue* = *K*.

Filtrate B.—Pass through filter water to just 500 c.c. Use 50 c.c. for Marsh's test (see *L*). If *As* is present, use balance for quantitative (see *C*). If not, evaporate small sample, dissolve in 10 c.c. water, add NH_4OH : blue = **Cu.**

C.—Heat balance of filtrate B to 80°C. and pass arsenic free H_2S[1] for two or three hours, until cool. Heat again, and repeat. Stopper and set aside in warm place for twenty-four hours. *Precipitate* may contain **As, Sb, Hg, Cu, Pb.** It may be used for the quantitative estimation of As, or for further identification by *D*. *Filtrate* = *I*.

D (*H_2S precipitate of C*).—Wash with H_2S water, warm with 4 c.c. ammon. sulphide, 4 c.c. ammonia, 8 c.c. water. Filter. *Filtrate* = *E*. *Insoluble* = *F*.

E (*Filtrate of D*).—Evaporate to dry; heat with HNO_3 till pure yellow; heat to expel HNO_3; add Na_2CO_3 and $NaNO_3$; fuse; extract with boiling water; add 2 Gm. $NaHCO_3$. Filter. *Filtrate* contains **As** and may be used for quantitative. The *insoluble* = **Sb.** (Apply tests.)

F (*Insoluble of D*).—Oxidize residue and filter in capsule with HCl and $KClO_3$; filter; dilute; heat; pass H_2S; filter; wash precipitate with warm HNO_3. *Filtrate* = *G*. *Precipitate* = *H*.

G (*Filtrate of F*).—Add 10 drops dilute H_2SO_4; evaporate; take up with water. *Residue* = **Pb.** *Filtrate* = **Cu.** (Apply tests.)

H (*Precipitate of F*).—Oxidize with aqua regia; evaporate; filter; dilute; test for **Hg.**

[1] H_2S purified by passing through water, calcium chloride and a tube, 30 cm. long, filled with alternate layers of glass-wool and iodine crystals.

I (*Filtrate of C*).—Use half for zinc, half for chromium.

Zn: Neutralize with KOH; acidulate with $H_2C_2O_2$; precipitate with H_2S wash precipitate with $H_2C_2O_2$ in H_2S water (1: 5); incinerate, precipitate and filter; dissolve in dilute H_2SO_4, plus a little HNO_3; evaporate dry; dissolve in H_2O; test for **Zn.**

Cr: Evaporate to just moist; mix with KNO_3; dry; fuse; dissolve; test for **chromate.**

K (*Residue of A*).—Fuse with KNO_3, Na_2CO_3, and NH_4NO_3. Suspend in H_2O; pass CO_2; boil; filter. Dissolve precipitate in dilute HNO_3. Test this solution for **Ag, Ba,** *and* **Pb.**

Marsh's Test (*see B*).—Produce hydrogen in flask by acting on pure zinc with arsenic free HCl; pass through $CaCl_2$, through tubes drawn out at several places. Heat to redness at the thick portion of a segment. (This blank test should be continued for six hours.) If no mirror appears, introduce the suspected solution. Black mirror occurs with arsenic or antimony. They may be distinguished as follows:

Arsenic	Antimony
Mirror *beyond* heated portion.	Mirror *at* heated portion.
Garlic odor on heating in air.	No odor.
Dissolves in hypochlorite.	Not.
Easily volatilized when heated in hydrogen.	Not easily volatilized.
Heated in air, yields easily volatilized white crystals.	Amorphous white residue, not easily volatilized.
Heated in H_2S, yellow, insoluble in HCl.	Red (black on strong heating); soluble in HCl.
Dissolved in HNO_3, evaporated, plus $AgNO_3$, plus vapor of NH_3, red or yellow precipitate.	No color in cold; black (metallic Ag) on heating.

GENERAL TREATMENT OF POISONING

While every case of poisoning demands to be treated by itself, yet certain general principles are all but universally applicable. These are the more important since the nature of the poison is so often unknown.

The first peculiarity of poisoning to deserve especial attention is the rapid course. This demands that whatever measures are taken, they *must be taken quickly.*

The pharmacist should therefore be thoroughly familiar with the general rules of treatment, so that no hesitation or delay occurs. On this account also, the antidote nearest to hand should be used in preference to one which can only be obtained with delay, even if the latter should be theoretically preferable.

The treatment of poisoning is directed against the cause and the symptoms. The former consists in *removing the poison*, or in *rendering it harmless.* Since neither of these objects can usually be attained absolutely, both are generally attempted at once.

Removal of the Poison.—The measures directed to this end must vary with the site to which the poison was applied.

On the skin and on accessible mucous membranes this will be accomplished by a thorough washing with water. This will also be useful by diluting the poison. If the poison is only sparingly soluble in water (as phenol) alcohol may be employed. Soap may be useful, but should be avoided if the poison is an alkali. The appropriate chemical antidote should also be added to the wash water (for acids or bromine: soap or linimentum calcis; for alkalies: vinegar or lemon juice). The poisons which are important in these situations are all irritants, and the further treatment consists in the application of oils or salves.

If the poison has been applied *hypodermically or to wounds,* the systemic effects may be lessened by preventing or retarding the absorption of the poison. The absorption can often be delayed sufficiently so that the drug is excreted as fast as it is absorbed, and doses which would otherwise be fatal may then cause no effect. The best means for this purpose is a firm ligature applied centrally to the wound. Where this is not feasible, sucking, cautery, or excision may be resorted to.

If an irritant poison has been *taken by the mouth*, the oral cavity and the pharynx demand the same treatment as would the skin.

With **gaseous poisons,** the treatment consists in free ventilation of the lung, using artificial respiration, and oxygen, if necessary.

Removal from the Alimentary Canal.—This is always the first step in the treatment of a case of poisoning by mouth, unless the symptoms are already so far advanced as to make it useless. Even if the poison has been administered some time before the treatment is begun, or if it has been given hypodermically, the alimentary canal should be cleansed, since many poisons (notably morphine) are excreted by this channel, and then again reabsorbed. The only contraindications to the emptying of the alimentary canal are: extensive corrosion, and advanced strychnine poisoning. Great caution and careful judgment are required in these cases.

The measures for the removal of poisons from the alimentary canal consist in emptying the stomach and intestine.

A *cathartic,* however, need only be administered after the acute manifestations are past. Oily cathartics should usually be avoided, and enemata are useless. The best purgatives in poisoning are the cathartic salts (15 to 30 Gm. of magnesium sulphate).

Evacuation of the Stomach.—The most effective—and in experienced hands, the simplest—method of emptying and cleaning the stomach is to wash it out with warm water, what is called *gastric lavage.* However, in unskilled hands, lavage might give rise to serious accidents, and it is not advisable for the pharmacist to take this responsibility—especially since he can usually attain the same object by inducing vomiting by using emetics, combining these with copious draughts of warm water.

Often the poison itself acts as an emetic—in this case,

water alone suffices. If vomiting does not occur spontaneously, it may often be brought on by tickling the fauces; but if this is not promptly effective, an active emetic should be given at once. Physicians usually prefer apomorphine, hypodermically. For the layman, mustard is the safest and often sufficient. Tartar emetic should *not* be used.

To Recapitulate.—*Lavage* deserves preference at the hands of the physician. It cleanses the stomach much more effectually, particularly of small insoluble adherent particles; it is less depressant to the patient; and it permits the convenient use of chemic antidotes. It is indispensable with depressant poisons which paralyze the vomiting center (such as deep morphine or chloral poisoning).

The complicated stomach pump has been generally abandoned for the more convenient stomach tube. In emergencies, 6 feet of rubber gas tubing, with a funnel attached, answers very well. The tube should not be *forced* down, but should be *gently* pushed to the pharynx, where the pharyngeal muscles will grasp it and push it further. Care should be taken to avoid overdistention of the stomach; it is much better to use small quantities of fluid frequently.

Emetics have the advantage of greater convenience, and avoid struggling. They should be repeated every fifteen to thirty minutes, if necessary.

Apomorphine—[5 mg. (grain 1/10) in 1 per cent. solution = 0.5 c.c. or ♏ *x*] hypodermically. This is the only emetic which can be given by the skin, and is therefore particularly useful if the patient resists. It is very prompt and certain, but rather more depressing than the following emetics:

Copper Sulphate or Zinc Sulphate.—These act promptly and with a minimum of depression, but should not be given if the poison is a corrosive. Zinc sulphate is less

irritant than the copper, and nearly as efficient; 2 Gm. may be given in a glass of water. The dose of copper sulphate is 0.5 Gm. at once, or three doses of 0.3 Gm., fifteen minutes apart. If it is ineffective it must be removed by lavage.

Ipecac.—A teaspoonful of the powder in water, or a tablespoon of the wine. Uncertain, and produces considerable depression.

Mustard.—A teaspoonful stirred in a tumbler of warm water. This is the most uncertain of these emetics, but useful in emergencies.

Chemical Antidotes.—Even lavage does not at once remove every trace of the poison, and vomiting always leaves a considerable proportion behind. It is therefore of considerable advantage to be able to render the poison harmless, permanently or even temporarily; and this can often be done by chemical means (antidotes).

The object of these is to render the poison incapable of acting, or of being absorbed. They accomplish this by enveloping the poison with an impenetrable coating, or by precipitating it, or by destroying it. Since these antidotes are hindered in their action by the presence of food, and since the precipitates are not perfectly insoluble, it is well to combine them with lavage or emesis, adding the antidotes to the wash water, or giving them in the interval between vomiting. They must be repeated frequently.

Demulcents (raw eggs, acacia, boiled starch or flour, milk, ad libitum).—These act by lessening absorption; by allaying inflammation; and in the case of metals, by precipitation.

Precipitants.—The most universally applicable of all precipitants is *tannin* (a teaspoonful of tannic acid, or preferably, very strong hot tea, ad libitum). The efficiency is increased by the addition of sodium bicarbonate, and diminished by alcohol and acids, since the precipitates are soluble in these media.

The *tannin* of coffee is useless; but ordinary tannin and strong hot tea are effective against certain alkaloids and metals; practically useless against others. The more important poisons against which they are especially *useful* are: strychnine, veratrum, digitalis, lead, silver, uranium.

Those for which they are practically *useless* are: morphine, atropine, cocaine, aconite, tobacco, As., Sb., Hg.

Scarcely useful against: Cocaine, brucine, aconitine, lobeline, nicotine, pilocarpine, codeine. muscarine, physostigmine, solanine.

Practically useless against: Atropine, coniine, morphine, As, Sb, Hg.

Of other, *specific precipitants,* the following should be remembered:

Alkaloids.—Tincture or compound tincture of iodine, 15 drops in half a glass of water.

Metals (especially mercury).—Raw eggs.

Arsenic.—Arsenic antidote (see Index).

Barium.—Sulphates (Glauber's or Epsom salt).

Oxalates.—Calcium (limewater, chalk, whiting).

Phosphorus.—Copper sulphate or oxidized (old) turpentine. (The former envelopes the phosphorus with an insoluble coating of metallic copper. Turpentine forms the insoluble turpentine-phosphoric acid.)

Antidotes Which Destroy the Poison in the Alimentary Canal.—(These, for the most part, will not be useful after the poison is absorbed.)

Acids.—Alkalies (burnt magnesia, soap, chalk, baking soda).

Alkalies.—Weak acids (vinegar, lemon juice).

Organic Poisons (Alkaloids, Glucosides, etc.) and Phosphorus.—Oxidizing agents, especially potassium permanganate, 2 grains to a tumbler, repeated as often as it is vomited; or for lavage, a liter of 0.05 per cent.

solution. Care must be taken that no undissolved crystals are administered. (In case of snake bite, the powdered permanganate may be rubbed into the wound, after free incision.) Hydrogen peroxide is another useful though less powerful oxidant.

Hydrocyanic Acid.—Permanganate, also arsenic antidote, hydrogen peroxide, and sodium thiosulphate ("Hypo").

Antidotes Which Destroy Absorbed Poisons.—To be effective, these must be given hypodermically or intravenously. The best known examples of this class are the antitoxic sera. The following are also useful: Sodium hyposulphite against hydrocyanic acid; and sodium carbonate against mineral acids.

Removal of Poisons after Their Absorption.—This can be attempted by increasing the excretions, but is usually not very successful. The elimination by the alimentary canal has been discussed. The principal remaining channels are the urine and sweat, of which the former is by far the more important.

Diuretics.—Water, especially as weak tea or carbonated drinks; theobromine, potassium acetate (irritant diuretics should be avoided).

Diaphoretics.—Hot drinks; heat; pilocarpine (if not contraindicated by pulmonary edema). Diuresis and diaphoresis often fail, partly because they act too slow, partly because not all poisons are eliminated by these channels.

Infusion of normal saline solution (1 liter of 0.9 per cent. injected under the skin) increases elimination by all channels. *Bleeding* may be resorted to in some cases. Up to a liter of blood may be drawn, a double quantity of salt solution being injected.

Symptomatic Treatment.—The symptoms produced by poisons can often be lessened or removed by the use of drugs having an opposite action. It is not to be supposed that these *physiologic antidotes* really lessen the action of the poison, although they cover its symptoms. But by tiding the patient over the dangerous period, and by preventing exhaustion, they are often potent means of saving life. It must be remembered, however,

that large doses of the antidotes often cause effects similar to those of the poison, which may add to the fatality of the latter. They must therefore be used in appropriate small doses.

It is not purposed to enter in this place into the special physiologic antidotes, but we shall take up only those measures which are generally useful.

These measures are directed, in the *order of their importance*, to: supporting the respiration, heart, and vasomotor tone; to lessen cooling, pain, convulsions and coma.

Respiration.—This is usually the first function to fail, and accelerates the other actions of the poison through the convulsant and paralytic effects of asphyxia, and by preventing the destruction of poisons through oxidation. For these reasons, it is well not to wait with the supporting measures until the respiration has actually failed, but to begin as soon as it shows signs of weakening. The measures consist in direct or reflex stimulation of the respiratory center; in artificial respiration; and in the administration of oxygen.

Reflex stimulation of the respiratory center is the quickest, but cannot be kept up as long as the direct stimulation. It may be secured by the administration of ammonia, by inhalation of ammonia water or smelling salts, or by aromatic spirits of ammonia (half a teaspoonful in a glass of water); the alternate application of heat and cold (whipping with wet towels); friction with alcohol, or camphorated oil; hypodermic injection of brandy, whiskey, or ether; mustard plasters.

Direct Stimulation of the Respiratory Center.—By strong hot coffee, strychnine (0.002 Gm.) or atropine (0.001 Gm.). The respiration may also be raised by improving the circulation. Saline infusion is also useful.

Artificial Respiration.—This should be practiced if the other measures are not promptly effective. It may be

used quite early in convulsive poisoning, since it lessens the tendency to convulsions and to fatigue.

Any of the common methods may be employed. The simplest and most effective (also in case of drowning) is that of Schaefer:

The patient is laid out flat, face down. The operator kneels or squats either across or one side of the subject, facing the head, and places his hands close together upon the back of the subject over the loins, the fingers extending over the lowest ribs. Leaning forward upon the hands, and keeping the elbows extended, he brings his weight to bear upon the subject, thus compressing the chest and abdomen, and expelling the air from the lungs. This pressure is applied gradually, not violently, for about three seconds; and is then released by the operator swinging his body back, but without removing his hands. The elasticity of the chest causes it to expand, and air is drawn in. After two seconds, the pressure is again applied, and so on, the operator simply swinging his body forward and backward every five seconds, or about twelve times a minute, without any violence and with very little exertion.

If the heart is strong, the artificial respiration should be intermitted occasionally for a short time, to see whether spontaneous respiration will be resumed.

Oxygen.—This will be useful in every case of failing respiration, and particularly if an asphyxiant gas is the cause of the poisoning.

Heart.—Attempts to revive or even to support the poisoned heart directly have not been very successful. The best results are obtained by the injection of normal saline, possibly with the addition of some epinephrine (1:100,000). Digitalis is usually unsuccessful. Strong rhythmical pressure (rate of 100 per minute) over the car-

diac region of the chest, may be helpful. A dilated heart can sometimes be revived by withdrawal of blood.

Vasomotor Stimulation.—This is usually accomplished by the reflex stimulants mentioned under respiration. Lowering of the head and bandaging the extremities is often sufficient.

Cooling.—This is prevented by the application of external heat; **pain** by morphine or if local, by cocaine; **convulsions** are controlled by the cautious inhalation of chloroform; **coma** by reflex stimulants, coffee, and atropine.

Methods of Administering Antidotes.—Physiological antidotes should be given hypodermically or intravenously, if possible. This obviates the loss of the antidote through vomiting, and the action is more prompt and more certain.

If the circulation is very low the absorption of hypodermic injections may also be very slow. It is therefore well thoroughly to massage the site of the injection, and if the circulation has almost stopped, to employ vigorous rapid rhythmical compression of the heart (this maintains a fairly efficient artificial circulation even after the heart has stopped beating).

Duties of the Pharmacist in Cases of Poisoning.—These cease with the arrival of the physician. Before this, however, the pharmacist should start at once whatever measures of treatment are, to his certain knowledge, indicated; for the success of treatment in poisoning is proportional to its promptness. The pharmacist should not take the responsibility of initiating any treatment unless he is certain that it is appropriate.

First, the administration of a chemical antidote is always in order, if the nature of the poison is definitely known.

Secondly, if the patient is not vomiting spontaneously, the administration of an emetic is indicated if it is known

positively that the poison was not a corrosive. In corrosive poisoning an emetic should *not* be used.

This is as far as the treatment by the pharmacist would usually be safe.

Any vomit should be preserved in perfectly clean vessels.

ANTIDOTE SET

INSTRUMENTS: HYPODERMIC SYRINGE; STOMACH TUBE WITH FUNNEL; HOT-WATER BAG

Drugs	Dose	Quantity
Ferri hydroxidum cum magnesii oxido	4 oz	U.S.P
Amyl nitrite pearls, 3 min	1	10
Apomorphine hydrochl., hypod. tab., 2 mg	2	10
Atropine s. hypod. tab., 1 mg	1	10
Caffeine citrated, 2 gr. capsules	1	20
Charcoal	Ad. lib.	2 oz.
Chloroform	Inhalation	4 oz.
Cocaine, HCl, sol. tab. 0.03 Gm	2 to 4 per quart	20
Iodine tincture	5 to 10 drops, diluted	1 oz.
Copper sulphate, powdered	0.25 Gm. diluted	2 drachm
Lime water	Ad lib.	Liter
Magnesii oxid. ponderos	Ad lib.	2 oz.
Pot. permang., 1 per cent. sol'n.	Dilute 20 times and give one tumbler	Pint
Sodium sulphate	Tablespoon, diluted	1 oz.
Sp. ammoniae arom	Teaspoon, diluted	1 oz.
Strychnine sulph., hypod. tab., 2 mg	1	10
Whisky	Ad. lib.	4 oz.
Olive oil	Ad lib.	Pint
Salt	Ad lib.	1 oz.
Soap, castile	Teaspoon	Cake
Starch	Ad lib.	Package
Dilute acetic acid	Tablespoon	4 oz.

HOUSEHOLD ARTICLES.—Boiled water, coffee and tea, strong, hot and black, eggs and milk.

Antidote Set.—To avoid delay, the usual antidotes should be kept together in one definite place; the bottles should be labeled with the usual dose; and their contents should be checked at least every month to insure their completeness and freshness.

Since the physician may be brought from the street, and thus may not have his instruments, these should also be included in the "*antidote set*" as shown on page 56.

CORROSIVE POISONS

When corrosive poisons are swallowed, they give rise to immediate and striking local effects, and these in turn to reflexes, shock, and often speedy death.

Local Effects.—These consist in destruction of the tissues touched by the corrosive. The surface of the lips and mouth is reddened, often bleeding and corroded; and corresponding changes occur in the esophagus and stomach.

Stains.—A number of poisons produce characteristic staining: yellow with nitric acid; mahogany with iodine; black with silver nitrate; blanched and "cooked" appearance with astringents, most metallic salts, formaldehyde and phenol; gelatinous with alkalies. Mineral acids blacken blood (especially in the vomit) by changing the blood pigment to hematin. Clothing may be stained red by most mineral acid; it may be "charred" by sulphuric acid.

Gastro-intestinal Symptoms.—The corrosion is accompanied by more or less intense pain in the mouth, esophagus and abdomen; and violent vomiting and purging, with straining. The vomitus and stools are often stained with blood; and with the acids, the blood is coagulated into a chocolate-colored, crumbly mass, the "coffee grounds vomit."

Reflex Effects.—The reflex effects consist in a general collapse: great anxiety, feeble irregular pulse; pale cold skin. Consciousness is preserved until near death (except with phenol).

Time of Death.—This varies greatly, depending largely not only upon the degree of corrosion, but even more on the tissues involved. Volatile corrosives—ammonia, hydrochloric vapor, bromine, etc.—may be fatal almost immediately by irritating and thus closing the slit of the larynx, and thereby shutting off the trachea (windpipe), and the air.

Late Death.—On the other hand, death may occur weeks after recovery from the acute effects. The destruction of the tissue may lead to scar formations; and by their contraction, these may shut off the esophagus, or other parts, more or less completely, leading to starvation.

Immediate Danger.—This consists mainly in perforation: the corrosion extending so deep that the stomach or intestines rupture, their contents escape into the abdominal cavity, and set up a general peritonitis, which is almost invariably fatal. This accident may easily be caused if a stomach tube is pushed against the partly corroded wall of the stomach; or even if the stomach contracts violently in vomiting. Hence the injunction against the promiscuous use of lavage or emesis in corrosive poisoning.

The General Treatment of Corrosive Poisoning.—This would consist in:

1. Diluting the poison.
2. The introduction of a demulcent.
3. Direct chemical antidotes.

The first two measures, and sometimes the third, are easily combined. As demulcent, one would use milk, thin starch gruel, white of eggs, any gum which may be

handy; sometimes olive oil. These demulcents are always indicated, and we need not repeat them in detail.

We may now proceed to the individual corrosives:

Mineral Acids.—These dissolve all organic matter, gradually but completely, the rapidity of action being proportional to the concentration.

Dilute Acids.—The official "dilute" acids are not corrosive, but still strongly irritant, and would upset digestion. Below 1 per cent. concentration, they do not irritate, unless they are used persistently; but even the most dilute solutions tend to dissolve the enamel of the teeth, which consists largely of calcium carbonate.

Treatment—The corrosive action is due entirely to the acidity and the concentration. The treatment therefore consists in diluting and neutralizing the acid.

Theoretically, any alkali could be used for this purpose, but practically it is better to avoid caustic alkalies—sodium or potassium hydroxide—since any excess would add to the corrosion. Potassium should be avoided since it may cause toxic effects. Carbonates and bicarbonates are somewhat dangerous, because the carbon dioxide which is evolved in the reaction might rupture the stomach. In an emergency, any of these may be used; but the ideal antidote is the heavy magnesium oxide. Next to this comes hard (castile) soap; washing soda; and calcium carbonate (chalk or whiting). They should be followed by the demulcents.

Acid Burns of the Skin.—These are common accidents. The acid should be immediately washed off with a solution of baking soda; and the burn then dressed with linimentum calcis, which combines the antacid lime with the protective oil.

Organic Acids.—*Acetic, citric, tartaric and lactic acids* act like mineral acids, but are much weaker. Poisoning ordinarily requires only dilution and demulcents.

Trichloracetic acid, on the other hand, is a powerful corrosive.

Oxalic acid and acid potassium oxalate are not only local corrosives, but act also systemically, by combining with the calcium of the body. These systemic actions result in damage to the heart, convulsions, and asphyxia. Death is therefore much more rapid than even with the mineral acids. Moreover, treatment by neutralization and dilution does not suffice; for this would serve only against the local, and not against the more dangerous systemic actions. It is necessary to precipitate the oxalate by lime. The soluble calcium chloride is the most efficient precipitant, but in its absence any available calcium compound may be used: chalk; whiting, plaster (set); mortar; milk-of-lime, etc.—whichever can be secured most promptly; for delay is dangerous. An emetic may then be given, if there is no blood in the first matter vomited.

Corrosive Alkalies.—The fixed alkalies, sodium or potassium hydroxide or carbonate, produce symptoms very similar to those of other corrosives; for instance, the acids: pain, vomiting and collapse. Their action, however, goes deeper, since they soften and gelatinize the tissues. The local appearance is therefore different from that produced by acids. The vomited matter has the color of chocolate rather than of coffee grounds. Death comes in about the same time; and there is the same or rather greater likelihood of dangerous contracting scars.

Ammonia.—When swallowed, this produces identical effects, with additional danger from its inhalation into the air passages. This may cause acute spasmodic closure of the glottis, and asphyxia; or bronchitis and pneumonia. One must be careful not to inhale too concentrated ammonia vapors in its therapeutic use, or similar accidents may follow.

Treatment of Alkali Poisoning.—The stomach tube should not be used, as the danger of perforation is especially great. The alkali should be neutralized by weakened acids. Vinegar and lemon juice are excellent as well as convenient. Eggs and a large quantity of oil or fat should be given for protection.

Systemic Actions of Potassium.—Lye and "salt of tartar" act not only as alkalies, but are toxic through their potassium. This has a paralyzing action on the nervous system, muscles, and particularly the heart. Ordinary doses of *potassium salts* do not produce these potassium actions, because they are very rapidly excreted; but these effects are witnessed with excessive doses. The most important toxic potassium salts are the nitrate and chlorate. These act also as local irritants, and damage the kidneys.

Potassium Chlorate.—This has a further dangerous effect, viz., it converts hemoglobin into methemoglobin, producing cyanosis and asphyxia. There is great difference in individual susceptibility, so that medicinal doses have produced serious effects. It should therefore never be used except on the advice of a physician. The treatment would be by evacuation and demulcents. Therapeutically, potassium chlorate is a mild astringent and antiseptic, used as a wash and gargle in inflammation of the mouth and throat, but it should not be swallowed. The lozenges are dangerous.

Lime.—Quicklime, CaO, is corrosive, partly as an alkali, and partly by abstracting water. Slaked lime is therefore much less caustic, the alkali action being rather weak on account of its limited solubility. Thus, lime-water is too weak to be poisonous. Burns of the eyes by particles of quicklime are common accidents. They are treated by washing the eyes with plenty of water and very weak vinegar (1:100). Sometimes they

are followed by opacities of the cornea which require prolonged treatment.

Irritant Gases.—The vapors of chlorine, bromine, sulphurous acid, the oxides of nitrogen; hydrochloric acid; ammonia, formaldehyde, etc.—all produce similar symptoms, arising from the irritation of the respiratory passages. When concentrated, they cause immediate closure of the glottis (the slit between the vocal cords), and hence speedy death from asphyxia. When more dilute, they lead to coughing, bronchitis, pneumonia.

The treatment consists in rapid removal of the gas by deep respiration of fresh air, preferably charged with steam. Chronic exposure to the more dilute vapors leads to malnutrition (cachexia).

Bromine.—This is a violent caustic, acting similarly to acids, but more penetrating and destructive. The treatment would be along the same lines.

Iodine.—The ingestion of iodine in substance or strong solutions is also corrosive, though not as intensely as bromine. It gives rise to a characteristic mahogany stain (which can be removed from the skin by ammonia or thiosulphate). The *treatment*, besides that common to all corrosives, includes the administration of starch in any form—flour or porridge—boiled starch being preferred. This must be followed by evacuation.

Iodism and Bromism.—The toxic effects of bromides and iodides are entirely different from those of the free elements. They occur especially after repeated administrations and consist in irritations of the mucous membranes—coryza (running at the nose), catarrh, gastric disturbances—and skin eruptions. Bromide also produces mental dulness. The susceptibility to these effects varies greatly. The effects are rarely dangerous. The treatment consists simply in withdrawal.

Volatile Oils.—These are strongly irritant, but not corrosive. *Turpentine* may be taken as a type. When swallowed, they produce violent irritation without direct destruction of tissue. The main symptoms are pain and collapse; vomiting and diarrhea; bloody and scanty urine. The strong intestinal irritation spreads also to the uterine organs, and may thus produce abortion. Tansy, savin, pennyroyal, etc., have been used for this purpose; but since the intestinal irritation is so much the stronger, the patient generally dies of gastro-enteritis before the object is secured. The volatile oils also have systemic actions after absorption. These consist in paralysis or convulsions, the effects resembling camphor.

Poisoning by volatile oils is treated by copious lavage or emesis, and administration of milk or mucilage for protection. Fixed oils are rather dangerous, since they favor absorption.

Formaldehyde.—The swallowing of concentrated formaldehyde causes prompt collapse, and suppression or bloody urine. As the tissues are not corroded, and as the formaldehyde itself is rapidly destroyed, the prospects for recovery are fairly good. The treatment is by lavage. The chemical antidote is dilute ammonia.

Coal Oil and Gasoline.—These produce relatively slight local irritation, and systemic symptoms resembling alcohol intoxication. The treatment is by lavage and demulcents.

Cantharides (Spanish Fly).—These produce the usual symptoms of non-corrosive irritation of the alimentary canal; but their main effects occur after absorption. They cause inflammation of the kidneys, which is often fatal. The urine is scanty, albuminous and bloody. The treatment consists in evacuation, demulcents, and administration of sodium acetate to *render the urine as bland as possible.*

After this rather lengthy excursion into toxicology, we may return to the medicinal uses of drugs.

We started our course with the locally acting substances, and first those which produce inflammation, the irritants. We then passed to the drugs which may be used to allay inflammation, and considered the emollients and demulcents. These, we found, act essentially by furnishing mechanical protection, useful especially in acute irritation. The next section comprises the astringents. These effect a chemical protection and stimulation, which is especially useful in the more chronic inflammations.

ASTRINGENTS

Actions.—Astringents are drugs that produce an astringent action, characterized by the peculiar "astringent" ("drawing together") taste, wrinkling, hardening and blanching of the mucous membranes, and hemostatic effect ("to arrest blood"); they also arrest excessive secretion of mucus (catarrh).

Mechanism.—These effects are all explainable on a common chemical basis, namely, the precipitation of proteins and similar substances, which is produced by all astringents. For instance, when an astringent—say tannin—is applied to a mucous membrane, it precipitates, first of all, the mucus, and thus forms a protective covering. Next, it penetrates between and coagulates the superficial layers of the tissues, which explains the hardening. The coagulated tissue tends to contract—hence the wrinkling and blanching. The coagulated tissue is also less permeable; hence less lymph and less secretions are formed, and thus the inflammatory processes are reduced. In case of hemorrhage, the coagulum occludes the vessels and thus arrests the bleeding.

Antiseptic Effects.—The astringents are also antiseptic, both because they tend to coagulate the protoplasm of the bacteria, and, mainly perhaps, because the coagulated secretions are not a favorable soil for their growth. Finally, the coagulation acts as a mild stimulant to the tissue cells, and thus increases their resistance, and may tend to favor repair.

Irritant Effects.—When the action of the astringent exceeds a certain degree, that is, if the coagulation is more extensive, it injures the vitality of the tissue, and thus causes irritation, necrosis (death of tissue), and corrosion. For this reason, most astringents, for instance the acids, silver nitrate, etc., can be used either to allay or to produce irritation, according to the concentration in which they are applied.

Extent of Action.—The effects of astringents are always superficial and therefore strictly local; for since they are precipitated and thus rendered insoluble, they cannot be absorbed into the circulation in active form. It is therefore quite irrational to expect any results at a distance; for instance, to expect astringent effects on the bladder by giving these drugs by mouth, or even hypodermically or intravenously.

Use in Hemorrhage.—Astringents were formerly used quite extensively to arrest hemorrhage; but this is now considered bad practice, except for very slight wounds. For these one may use tannin, alum, or the inorganic iron salts. But if the hemorrhage is at all extensive, so much of the astringent would be required that it would be irritant, and would seriously interfere with natural healing.

Catarrhs.—The greatest usefulness of astringents lies in the treatment of subacute or chronic catarrhal inflammation of mucous membranes—sore throat, diarrhea, bladder trouble, etc., which will be discussed presently.

Vegetable Astringents.—The practically useful astringents may be conveniently grouped under two classes, *metallic and vegetable.* The vegetable astringents owe their activity to the tannins—substances that occur in very many plants.

These drugs are more useful than pure tannin for internal administration, especially in diarrhea; for the pure tannin would exert its main action on the stomach, where it is detrimental, leaving very little for the intestine, where it is needed. In the crude drugs and extracts—such as gambir, kino, krameria, and many others the tannin is so enveloped by gums, resins and other extractives, that its action is delayed until it reaches the intestine.

The same result can be secured by precipitating the tannin with various proteins. These precipitates—tannalbin, etc.—are practically insoluble and hence inactive until the protein component has been digested. This extends their action into the intestine.

Tannin, it will be recalled, precipitates many metals, alkaloids, and some neutral principles, and is therefore a useful antidote to these. It has the advantage that it is entirely harmless, and can be given in practically unlimited amount. The precipitates are somewhat soluble, however, especially in the presence of acids and of alcohol. The stomach should therefore be emptied as speedily as possible.

The Treatment of Diarrhea.—We may here permit ourselves a short excursion into the general treatment of the common disease—diarrhea; for this may serve to illustrate the general principles of scientific treatment, as well as the limitations and possible dangers of the common practice of self-medication with patent medicines.

Causation.—Diarrhea—loose stools—is not really a disease in itself, but is a symptom which may arise in

many conditions in several different ways. For instance, while it is usually due to indiscretions of diet, these may work in two ways—by being indigestible or spoiled. Spoiled food may act either through infection with its bacteria or by the chemical products or ptomaines produced by these bacteria. While food is the most common cause, there are many cases which arise independently—for instance, typhoid, cholera, tuberculosis, chronic arsenic, etc.

Objects of Treatment.—Diarrhea therefore gives little or no indication of what is wrong with the patient; and it is an axiom in therapy that the patient is not cured until the *cause* of his illness be removed. He may indeed be *relieved* by removing the superficial symptoms; this in itself *may* be useful sometimes; but in other cases it may be distinctly harmful. For it may seriously interfere with the efforts of nature to establish a spontaneous cure. To be successful, the therapeutist must work *with* nature, not against her.

This is well illustrated by the very subject under discussion. Diarrhea, when due to indigestion, is simply an effort of nature to get rid of harmful material. The first object or indication is therefore to help nature in this effort by a cathartic. This done, the persisting irritation should be relieved. This may be accomplished with chalk, bismuth, astringents, antiseptics or opium, or by a combination of several of these.

Chalk.—This acts mainly by neutralizing the excessive acidity which results from intestinal putrefaction. It also furnishes some mechanical protection as a "dusting powder." It is also conceivable that the calcium allays further the irritability of the intestines.

The Basic Bismuth Salts.—These also act as antacids and protective powders. In addition, they bind the hydrogen sulphide—another very irritant product of

putrefaction. Further still, a minute quantity of the bismuth enters into solution, and this acts as an astringent and antiseptic.

Astringents.—If the astringent effect is the main object, tannin is given in the form of vegetable extracts, or tannin albuminates. These act in the manner explained; they constrict the blood-vessels, diminish exudation, and form a protective precipitate over the mucous membrane which helps to exclude the irritant products. They also help to reduce putrefaction and fermentation, by coagulating the food material.

Antiseptics.—These lessen the putrefaction and fermentation by injuring the microörganisms. In order that they may reach the seat of the trouble, they must be fairly insoluble, so as to pass the stomach without being absorbed. *Betanaphthol* and *phenylsalicylate* are the classical examples. The last is practically inactive in itself, but the pancreatic ferments and alkaline intestinal juice saponify it into phenol and sodium salicylate which are both antiseptic.

Opium and Morphine.—These act by quieting the intestinal movements. They do this largely by slowing the discharge of food from the stomach. In this way, the inflamed intestines are rested; and what food does reach them is more perfectly predigested in the stomach, therefore more readily absorbed, and therefore less liable to decomposition. Opium is the more effective, since the extractives delay the absorbing of the morphine, thus keeping it longer in the stomach, where its action is exerted.

Diarrhea mixtures are all constructed along the above lines. They are effective so far as the symptoms of diarrhea are concerned, but whether they are useful or harmful, and whether and when their use is justified—

this requires experience and foresight which taxes to the full the knowledge of a skilled physician.

If the diarrhea is not due to indigestion, but to some other disease, the ordinary treatment is certainly harmful, directly and indirectly, by delaying the right treatment until it may be too late—for instance, in typhoid fever.

The Metallic Astringents.—The most important examples of these are zinc sulphate, copper sulphate, silver nitrate, ferric chloride, alum, and lead acetate.

The use of these is almost entirely local: on the skin or open sores; on accessible mucous membranes, such as the eye or mouth; and by injection in the urethra, bladder, vagina, etc.

They are employed for the purpose of checking the inflammatory process, by their astringent and antiseptic action—the majority being actively antiseptic. Their employment should generally be deferred until the acute stage of the inflammation is past, since they are somewhat irritant. They are also employed as *styptics*, to stop bleeding. Alum and iron may be used in the mouth; the others should be avoided if there is any danger of their being swallowed. Lead should not be used continuously, since it may produce chronic poisoning, even when it is applied to the skin.

The Treatment of Pharyngeal and Laryngeal Catarrhs or "Sore Throat."—These were formerly treated with active, more or less violent, styptics and antiseptics, such as the popular gargle of ferric chloride and potassium chlorate. These are sometimes useful, without doubt, but modern physicians consider their indiscriminate use as more often harmful, and potassium chlorate is known to be distinctly dangerous to some individuals. The home-treatment of "sore throat" presents the danger

that very serious conditions, such as diphtheria, may be overlooked until it is too late.

The modern practice consists in the treatment of the infection by mild and harmless antiseptics, such as hydrogen peroxide; and in the meantime soothing the irritation by mild alkalies, such as sodium borate or bicarbonate, and by glycerine. The employment of more active astringents is limited to special cases, particularly those of a chronic type.

Cleanliness of the mouth tends to prevent its infection. *Mouth washes* should be alkaline, to dissolve the mucus and protect the teeth. This may be accomplished by borax, which is at the same time slightly antiseptic. However, it is useless to expect any direct germicidal effect in the mouth—partly because germicidal concentrations would be poisonous, and partly because a mouth wash does not remain long enough in the mouth to act upon the bacteria. "Liquor antisepticus" and "liquor antisepticus alkalinus" are, therefore, misnomers.

Nasal Douches.—The mucous membrane of the nose is very sensitive, and it is therefore necessary to make applications as non-irritant as possible. This may be accomplished by the use of oil, or of "normal saline" solution. The latter contains 0.85 per cent. of NaCl. (Formerly 0.6 to 0.75 per cent. were used. The latter concentrations are indifferent for frog's tissue, but not for man.) The addition of ½ to 1 per cent. of sodium bicarbonate or borate is useful for their alkaline or antiseptic effect.

Nasal douches should not be advised indiscriminately, because they are apt to wash infection into the deeper cavities of the nose. This can be avoided by the use of atomized sprays, having a similar composition.

Boric acid and borax are used on mucous membranes in

concentrations of 1 to 4 per cent. Both are antiseptic, the boric acid much more so than the borax. The acid is astringent, and therefore tends to heal catarrh; while the borate dissolves the mucus and is more useful as a cleanser.

Eye Waters.—They may contain 2 per cent. boric acid as a basis. If a more astringent effect is desired, ½ per cent. of zinc sulphate may be used; or in painful conditions, 1 per cent. cocaine. The use of the last should not be prolonged. Rose-water is rather more pleasant than plain water. Collyria should always be filtered.

The Treatment of Hemorrhage.—The entire body is permeated by a closely packed network of blood-vessels. These are tubes of various caliber that convey the blood from the heart to the organs—the *arteries*—and from the organs back to the heart—the *veins*—and the finest hair tubes or "*capillaries,*" which join the arteries and veins.

If a blood-vessel is severed, the blood escapes and is lost to the body. If the loss were not checked, we would bleed to death from the smallest wound. To prevent this, nature has provided the process of coagulation. Very soon after the blood escapes from its vessels, it loses its fluidity, and sets into a jelly-like "clot," which covers the bleeding area, and so stops the vessels.

This process requires a few minutes, however, and in the meantime, much blood may be lost. Moreover, the clot has a rather weak consistency, and is therefore easily broken or dislodged, by movements of the patient, or even by the *blood-pressure.* This pressure is only slight in the veins; but very considerable in the arteries. *Arterial hemorrhage* is therefore recognized by the high spurting of the blood, which pulsates with the heartbeats; and the blood has an arterial color. In *venous hemorrhage* the blood wells up continuously, and is dark colored or blackish.

Hemorrhage from a large artery can be controlled only by shutting off the blood-pressure; that is, by compressing or tying the artery on the side toward the heart. In an emergency, the first measure will be to place a finger firmly on the bleeding point. Next a bandage or handkerchief is tied as tightly as possible (around the arm, for instance), above the bleeding point; and this bandage is further tightened, if necessary, by twisting it with a stick or ruler. The physician when he arrives will tie the artery with a ligature.

If the blood does not spurt, these methods are not needed; in this case, the object of treatment will be to favor the formation of the clot. All astringents form a chemical clot, by precipitating the blood; they are therefore effective in capillary and venous hemorrhage and their use as *styptics* is ancient. Formerly, people were satisfied with meeting the immediate symptoms in this way. When surgeons began to inquire into the ultimate results, they found that the styptics are apt to do considerable harm. The astringents, when used in effective concentration, injure the tissues more or less; hence the wound is apt to become infected; to heal more slowly, and not so cleanly; by "granulation" rather than by "primary union." Also, the chemical clot often becomes detached and the "secondary hemorrhage" which results is difficult to control. The astringent styptics should therefore be used only in slight and superficial wounds.

The modern treatment of bleeding is entirely mechanical, combined with cleanliness. The first indication is firm pressure with aseptic cotton—the pressure closing the vessels, while the fibers of the cotton hasten the clotting. The popular cobwebs act in the same way —but are pretty sure to convey infection. The bleeding point is kept as high as convenient to utilize gravita-

tion. The application of ice is also useful. In nosebleed (epistaxis) the nose is packed with cotton. Slight hemorrhage may be temporarily arrested by epinephrin. For internal hemorrhages, the best treatment is to keep the patient quiet by morphine.

Hydrastis may be briefly discussed here. It is used in catarrhs and hemorrhages, somewhat in the same way as the astringents, but is probably much less effective. It contains the alkaloids berberine and hydrastine, with related actions. From hydrastine is prepared the artificial alkaloid, hydrastinine, whose action is also similar. Perhaps the real main use of hydrastis is as a bitter stomachic in gastric catarrh and other dyspepsias. It also causes contractions of the uterus.

Toxicology of the Astringent Metallic Salts.—The toxicology of the soluble salts of all the metals is very similar, and can be discussed in common. Lead, arsenic, antimony and mercury show some peculiarities and are so important as to merit separate consideration. We shall therefore refer now mainly to zinc, copper, silver, tin, aluminum, nickel, bismuth and iron; but, in fact, what we shall say in regard to them applies also to all the other metals. The main differences are in relative toxicity, and this is mainly due to different absorbability.

The metals mentioned all possess a relatively low toxicity. The insoluble salts are scarcely toxic. The soluble cause mainly gastric irritation—vomiting, pain, collapse—but the symptoms are not nearly so violent as with acids or alkalies. Death may, however, ensue from large doses.

Treatment of Poisoning by Metallic Poisons.—The metallic poisons should be diluted with water, or better milk, and the stomach emptied. They generally cause vomiting, but if not, this should be encouraged by non-irritant emetics, especially apomorphine. Washing the

stomach would be still better. At the same time, the metals may be precipitated either by protein or tannin (these two classes of antidotes should not be used together). As protein, one should give half a dozen *raw* eggs, or the whites alone. With tannin, it is useful to add an alkali—baking soda, chalk, or magnesia. Alkalies should not be given if eggs are used. In poisoning by silver nitrate, common salt is the best chemical antidote. In copper poisoning, potassium ferrocyanide may be given. It must be remembered that the use of the chemical antidotes does not dispense with emptying the stomach.

Bismuth-poisoning.—The soluble bismuth salts are markedly corrosive and toxic; the insoluble salts are generally harmless by mouth even in large doses; but under special conditions they may give rise to slow poisoning, namely, when they are freely applied to open sores and to sinuses (channels). The symptoms then resemble both chronic arsenic- and lead-poisoning.

Large doses of bismuth subnitrate have sometimes given rise to acute poisoning, due not to the bismuth, but to the nitrate, which may be reduced to the poisonous nitrite in the intestines. It is therefore better to use the subcarbonate when large doses have to be given, as in *x*-ray work.

Copper.—This is but little toxic to the higher animals, although it is very destructive to the lower forms of life, particularly algæ, so that it may be employed for the purification of the water supply. In man, very minute quantities (such, for instance, as are used in coloring vegetables) usually produce no noticeable effects; larger doses simply produce vomiting, by which they are completely expelled.

Lead-poisoning.—Acute lead-poisoning is rather rare. The symptoms resemble those of other metals, except

that there is more constipation. Its treatment would also be similar with the addition of sulphate. As a chemical antidote sodium sulphate or magnesium sulphate may be used.

Chronic lead-poisoning is a very important disease. It may follow acute poisoning, but is more commonly caused by continued exposure to small doses of lead in various trades, especially those in which lead paints are used. The excretion of lead is very slow, so that the metal tends to accumulate in the body with every exposure until the disease finally breaks out. One should therefore be on his guard against introducing lead in any form into the mouth. The cleaning of bottles with shot, tinfoil wrapping about food, the lead in the solder of canned foods, etc., are among the insidious ways in which lead may find its way into the body.

The disease is a very serious one, but fortunately disappears in most cases if the patient is removed from further exposure. The most common symptoms are the characteristic black line—lead line—at the junction of the teeth and gums; obstinate constipation; violent colic attacks; muscular paralysis, particularly "drop-wrist;" high blood-pressure; gout; anemia, etc. The treatment of chronic lead-poisoning lies in the province of the physician.

Barium.—This may be considered here since some of the symptoms of acute barium-poisoning resemble somewhat those of chronic lead-poisoning—colic, high blood-pressure. There are also diarrhea, convulsions, and poisonous effects on the heart, resembling those of digitalis. Barium salts are highly toxic. The treatment consists in sulphates and emetics.

It is interesting to note that the very closely related *strontium* is harmless.

ANTISEPTICS AND DISINFECTANTS

Microörganisms.—A new world was opened to us by the scientific labors of Pasteur; by his discovery of the microscopic mould or yeast-like organisms which are the cause, according to their kind, of all putrefaction; of many diseases, for instance, all those which are contagious; of the infection of wounds; of many kinds of fermentations, such as acetic, lactic, etc. The majority of these microörganisms belong to the class of *bacteria*, very minute (one-celled) plants. Those which are practically globular are termed *cocci*, while those which are elongated, more or less rod-shaped, are called *bacilli*. There are also other morphological varieties, but their classification and identification are based mainly upon the physiological characters—upon the chemical changes which they produce, upon the specific fermentations, diseases, etc. Certain fermentations (for instance, the alcoholic) are produced by the related *yeasts;* and certain diseases (for example, malaria, syphilis, etc.) by the related *protozoa* or one-celled animals.

Conveyance of Bacteria.—In order to produce their effects, the microörganisms (or their products) must be actually present. The minute size of these organisms facilitates their conveyance from one object or person to another. Many of them are carried in the air (tuberculosis) or water supply (flies and typhoid). Insects often convey the contagion by mere contact (typhoid by flies), or by their bites (plague by fleas). Some protozoa have a complicated life cycle, which requires that they pass through a certain second "host" before they can reinfect the first. In this way, the mosquito is essential to the conveyance of malaria.

The air practically always contains bacteria; but these are not necessarily pathogenic (disease-producing). So long as bacteria are moist, they do not pass into the air;

it is the dried bacteria—the dried sputum, etc.—which are dangerous in this connection. Careless coughing, however, conveys them in a spray, which soon dries.

These discoveries of Pasteur and his many eminent followers are of such great practical importance that they have become a vital part of our everyday life. It is difficult to realize that they were unsuspected only half a century ago. As is so often the case, however, empirical experience had anticipated scientific discovery. The phenomena of fermentation, putrefaction and disease were of course always known, though they were not explained. It was also known that certain substances and processes which we now know as antiseptics check fermentation and putrefaction. Drying, salting, freezing and smoking were used for preserving food—the ancient mummies of Egypt are a remarkable tribute to the empirical art of antisepsis.

Useful and Harmful Bacteria.—Some bacteria are highly useful. Indeed they are indispensable to the persistence of life on the globe, for they are the agencies that return dead material into forms in which it again becomes available for food. Without the putrefactive microörganisms, all vegetation, and hence all life, would be arrested.

Other bacteria, however, are equally potent for harm —the "spoiling" of organic materials causes incalculable financial losses; but the greatest harm of bacteria to man lies in the production of disease. All infectious and contagious diseases, pus formation, etc., are caused by microörganisms, and mostly by specific bacteria. Some, such as malaria, syphilis, and a number of others are produced by similar microörganisms, the protozoa, which are generally counted in the animal kingdom, the divisions being somewhat arbitrary.

It is not an exaggeration to say that the progress of

civilization depends chiefly on the control of the microörganisms—on our ability to destroy them when and where this may be desirable. This subject is therefore of vast importance to humanity.

The control of microörganisms comes properly under the headings of asepsis, antisepsis and disinfection.

Asepsis means the exclusion of bacteria; antisepsis, the checking of their growth; disinfection, their destruction.

Asepsis.—Dry bacteria are so light that they are raised like the finest dust, remain suspended in the air, and thus gain access to everything which is exposed to the air. If they find moisture and congenial food, they proceed to multiply with great rapidity. The most practical way of excluding them, say from a bottle or wound, is by a thick layer of dry cotton, the meshwork of fibers serving to entangle the bacteria. This, of course, would do little good if the surface is already infected. It must therefore be preceded by thorough cleansing—for ordinary dirt means bacteria—by sterile fluids; or the bacteria must be destroyed by heat or chemical means. A surface or fluid which is thus cleansed is said to be aseptic, or sterile.

The Destruction of Bacteria.—Bacteria are living cells, consisting of protoplasm and therefore containing proteins. Consequently they may be killed by anything which destroys protoplasm, or which coagulates or dissolves, or otherwise alters proteins. However, their resistance is relatively greater than that of most cells, and in this lies the special difficulty of effective disinfection, especially in the tissues of the living body, which generally succumb to injury much more easily than do the bacteria. Outside of the body, the destruction is much more simple. The two problems must therefore be considered separately.

Disinfection Outside of the Body by Heat.—Consumption by fire is of course an absolutely sure means of destroying bacteria. It should be used where it is practical but it is too destructive to other things to have a universal application. Next comes destruction by more moderate heat. Of this, the most effective form is superheated steam—115 to 120°C. for fifteen minutes. Dry heat is much less effective, requiring two hours at 160° to 170°C. Simple boiling, for from five to thirty minutes, destroys most disease-producing bacteria; but it does not absolutely kill a number of those which produce undesirable fermentations, particularly those which have the property of forming "*spores.*" These are a highly resistant phase of the life circle of certain bacteria. They may be reached by the process of "fractional sterilization." In this, the material is heated for a short time daily, for a number of days. Each heating will kill the developed bacteria, and the spores will then develop and be killed by the next heating.

With certain foods, particularly milk, actual boiling is undesirable, because it alters the flavor, and possibly renders it less digestible. In this case a lower degree of heat is employed, "*Pasteurization.*" This destroys most of the objectionable bacteria, but not all.

Glass vessels and similar articles are usually sterilized by strong dry heat. Surgical instruments and other metal utensils are sterilized by boiling in a solution of sodium carbonate. This renders the sterilization more effective, and at the same time it prevents rusting.

Chemical Disinfection.—A large variety of substances can be used for this purpose, outside of the body. We will mention only the most important, and their principal applications:

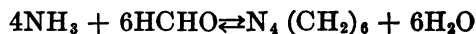
Formaldehyde.—This is a very powerful disinfectant. In the form of vapor it is used to disinfect the sickroom

after infectious diseases. The vapors are most conveniently produced by the interaction of formaldehyde solution and potassium permanganate. They may also be formed by burning methyl alcohol in special lamps; or by suspending sheets saturated with the solution. Boiling of the solution is not a good method, since the heat converts a large part of the formaldehyde into the difficultly volatilizable trioxymethylene (paraform).

Formaldehyde-Permanganate Method.—For a room of 2000 cubic feet, 2 pounds of potassium permanganate are placed in a 3-gallon pail, and this is set in a large tin can containing water. When everything is ready, 2 quarts of 40 per cent. formaldehyde are poured on the permanganate, the room is vacated immediately, and left closed for at least twelve hours, then thoroughly aired (Hoxie).

Following a suggestion of Rosengarten, S. G. Dixon, 1914, advises a chromatic mixture for vaporizing the formaldehyde: A solution of 1½ fluid ounces of concentrated sulphuric acid and 1 pint of U.S.P. formaldehyde solution is prepared in advance and keeps perfectly. When needed, it is poured on 10 ounces of sodium dichromate crystals, which have been spread in a thin layer in a vessel of ten times the capacity of the ingredients. The gas is liberated more rapidly than with permanganate; the operator must therefore withdraw promptly.

The vapors of formaldehyde are extremely irritant, so that the room cannot be occupied so long as they are present. They may be quickly removed by evaporating some ammonia, which combines with the formaldehyde to form the non-irritant hexamethylentetramine:

$$4NH_3 + 6HCHO \rightleftarrows N_4(CH_2)_6 + 6H_2O$$

Formaldehyde solution is also useful for disinfection

of the excreta, fecal and urinary matter, garbage, etc., anything in which it need not be inhaled. For this purpose 5 to 10 per cent. of the commercial solution are left in contact with the material for at least an hour.

Formaldehyde is totally unsuitable for application to the body, since even very dilute solutions are irritant and injurious. Its use as a food preservative, especially in milk, is rightly prohibited by law.

Hexamethylenamine.—This is a derivative of formaldehyde; but it occupies a very different position. It is neither irritant nor antiseptic, and passes through the body practically unchanged. In the presence of acid, however, and therefore in the urine, it is very slowly decomposed, with the liberation of minute quantities of formaldehyde. These are generally too small to be irritant, although irritation of the urinary bladder does occur occasionally. However, the continuous liberation of formaldehyde, even in this small amount, suffices to check the growth of bacteria, so that the urine becomes antiseptic. This is utilized in cystitis (inflammation of the bladder) especially to guard against infection of the bladder after operations, etc.

Phenol, cresol, and mercuric chloride will be considered later.

Caustic Lime.—Slaked or unslaked lime is a cheap and effective disinfectant for excreta, refuse, etc., and in the form of whitewash, for walls. To be of any use, it must be fresh; for the carbonate into which it is converted on exposure, is useless.

Chlorinated Lime.—This owes its activity mainly to the chlorine which it liberates, slowly on moistening, rapidly on the addition of acid. It is very effective on direct contact; and the calx chlorinata is one of the most effective safe germicides adapted for all uses outside of the body, except such as are precluded by its corrosive

and bleaching action. To be effective, however, it must be in actual contact—the chlorine which escapes into the air is not sufficiently concentrated to be of any use, although it may serve to hide more disagreeable odors.

For the disinfection of excreta, 6 ounces of the "chloride of lime" are mixed with a gallon of water; a quart of this is added to each discharge and allowed to stand for an hour.

Chlorinated lime is also used for the sterilization of drinking water. From 5 to 15 pounds to several million gallons are effective, but impart a noticeable taste.

Nearly neutral solutions of *hypochlorous acid* are being used for wound antisepsis (*Carrel-Dakin antiseptic*).

Deodorants.—One must be careful not to fall into the common mistake that the removal of the odor of putrefaction stops the putrefaction itself. This mistake may be very dangerous. Most disinfectants are deodorants; but other substances may cover up disagreeable odors, or even destroy them, without touching the underlying putrefaction. Such deodorants may be useful, esthetically, provided that they do not induce a false sense of security.

Ferrous Sulphate—Copperas or Green Vitriol.—This is a good example of a deodorant, which is practically not antiseptic. Putrefaction odors arise largely from the formation of sulphides and of ammoniated substances. Both of these are bound by the iron salt, with the formation of iron sulphides and ammonium sulphate.

Sulphur Dioxide or Sulphurous Acid.—This is another substance whose efficiency is overestimated by popular judgment. It is formed by the combustion of sulphur (3 pounds per 1000 cubic feet of space). It has a very disagreeable odor and a powerful bleaching effect. It was employed for the disinfection of rooms after sickness, but has now been replaced by the more reliable

formaldehyde. For killing insects, however—for instance, the mosquitoes of malarial or yellow fever—the sulphur dioxide is by far more effective.

Sulphites.—These are sometimes used to bleach and preserve food products. This is excused on the ground that they are converted into the harmless sulphates; but as one cannot be certain of the completeness of the conversion, and as even small quantities of sulphites are demonstrably harmful, their indiscriminate use is not justified.

Food Preservation.—Foods and drugs which contain organic matter tend to "spoil" when they are exposed in a moist state to bacterial infection, and thereby become unfit for consumption. To preserve them, the bacteria must be excluded, as far as possible, by cleanliness; and the remaining bacteria must be destroyed, and reinfection prevented. Heat is the best, certainly the least harmful means for destroying such putrefactive bacteria, but it often causes chemical changes that are undesirable. It does not protect the substance against reinfection. It is also more or less troublesome to apply. Hence, the tendency to use chemical preservatives, which require no skill and whose action is permanent. Alcohol, acetic acid, glycerine and sugar have the sanction of use in galenical preparations, and are here generally unobjectionable, if not desirable. In food products, the question is not so simple, for food being consumed in larger bulk, relatively large quantities of the antiseptic would be introduced into the body, at least under some circumstances.

The presumption is certainly against chemical food preservatives. To justify their use, it would need to be proven, beyond reasonable doubt, that they are entirely inactive, in the largest quantity which could possibly be taken in food, if these quantities were continued daily and

indefinitely, by diseased and predisposed individuals as well as by the healthy. Such proof would be very difficult to bring. It stands to reason that chemicals which are sufficiently powerful to restrain bacteria, would presumably also have some deleterious effect on the human organism. If it is difficult to show such harmful effects conclusively for some of the mildest preservatives, such as boric and benzoic acid, or for saccharin, this could fairly be attributed to our limited means for discovering slow cumulative changes, rather than to the absence of such changes.

Altogether the interests of public health demand that chemic food preservatives be prohibited, except under special circumstances. Permitting their use on condition that the quantity be stated on the label is scarcely a sufficient protection, since the public has not the information to appreciate their insidious dangers.

Chemical Antiseptics Applicable to the Surface of the Body—Skin, Mucous Membranes, Wounds, Etc.—It is practically impossible really to kill the bacteria on the surfaces of the body, much less those which have entered into the cells. This failure is due to two causes. In the first place, really germicidal concentrations would destroy the tissues. Secondly, the chemical antiseptics are weakened enormously by the presence of proteins and other cell constituents. It is possible, however, to reach concentrations which, while they do not kill bacteria, still injure them more or less; and for practical purposes this is no small achievement. The resistance of the tissues and the virulence of the bacteria are often so delicately balanced that a very small advantage may turn the scale. It makes little difference, in practice, whether the disinfectant actually kills the bacteria, or whether it simply weakens them so that they can be killed by the body cells and juices. Even if the bacteria

remain alive, this does little harm so long as they do not multiply.

These considerations have an important practical bearing on the relative value of the different antiseptics. Evidently, their germicidal action on pure cultures of bacteria is far from being the sole determining factor in their practical efficiency; for their practical usefulness is also influenced by the effect of the agent upon the vitality of the tissue cells; by the influence of organic matter; by the penetration, and by other factors.

The relative efficiency can only be estimated by taking all these matters into consideration, and will vary under different conditions. An agent which is of relatively great value in the urethra may be of relatively slight value on the skin. Statements of "relative efficiency" can therefore only be along the most general line. In this sense, the following will give as fair a general idea as is obtainable. It must be understood that each antiseptic must be used in proper concentration and under suitable conditions.

RELATIVE EFFICIENCY OF ANTISEPTICS

First rank: Mercuric chloride; formaldehyde.

Second rank: Silver nitrate; iodine; phenol; permanganate; hypochlorous acid.

Third rank: Hydrogen peroxide; boric, salicylic and benzoic acid.

Fourth rank: Bismuth salts; iodoform.

Fifth rank: Alcohol; sugar; glycerine; salt; saltpeter.

The last (fifth) class acts by dehydrating or coagulating the material upon which the bacteria feed. Their direct action on bacteria is small, and they are therefore effective only as long as they are present in fairly high concentration.

Some of these antiseptics may be discussed more fully in this place; the others will be considered in other connections.

Hydrogen Peroxide.—This is fairly efficient, very slightly irritant, and absolutely non-toxic. It is therefore suitable as a mild antiseptic for mucous membrane, especially in the mouth. It owes its activity to the nascent oxygen which is liberated in contact with organic matter. This liberation is especially lively in the presence of pus; and the frothing serves to dislodge the pus, secretion, crusts and dirt, so that it has considerable value as a cleansing agent. On the other hand, if the gas cannot escape, it may do mechanical damage. For this reason the peroxide should not be injected into partly closed wounds, fistulas, etc.

Hydrogen peroxide is also a good and relatively harmless bleaching agent.

Certain *organic peroxides* (benzoyl, etc.) have been used as intestinal antiseptics in typhoid fever, etc. Their efficiency for this purpose is doubtful.

Iodoform.—This is employed as an antiseptic dressing for open wounds. Its antiseptic value is very slight in test-tube experiments; and some surgeons also deem it of little use clinically. The majority, however, believe that it promotes healing. It is quite conceivable that this may occur—either by the liberation of iodine, or by stimulation of the bactericidal properties of the tissues; or by stimulation of growth and repair. The question is not settled.

The iodoform has disagreeable qualities—its persistent and penetrating odor and the production of systemic poisoning, when it is applied to large open surfaces. These drawbacks have led to the introduction of substitutes, particularly of other insoluble organic iodine compounds, such as thymolis iodidum, (dithymoldiiodide

or aristol). However, the substitutes have been found rather disappointing in practice.

Iodoform poisoning may take two forms: convulsions and coma; or more commonly skin eruptions and coryza, resembling iodism.

Phenol (Carbolic Acid) is one of the most popular antiseptics, and also one of the most popular suicidal poisons. As an antiseptic, it has the advantage over "sublimate" that it penetrates rapidly and deeply, and acts fairly well even in the presence of organic matter. Its antiseptic value is high, even when it is fairly dilute; but much higher concentrations are needed to make it germicidal.

Local Actions of Phenol.—These are twofold; irritant and sensory. Both may be noted on the skin. The application is followed by tingling and later by anesthesia. The irritant effects are first shown by blanching and wrinkling. With higher concentrations and prolonged contact, the tissues are killed, and become gangrenous, but there is no direct corrosion. The pain is relatively slight, because of the partial anesthesia. A drop of concentrated phenol is a convenient disinfectant for bites and other small deep wounds, where real corrosives are too painful.

The degree of local necrosis depends largely on the length of contact. A short application of absolute phenol may be quite harmless, while the continuous application of a 5 per cent. solution has repeatedly caused gangrene.

This indicates the proper treatment of phenol "burns," namely, prompt removal. Any good solvent of phenol such as alcohol, glycerine, oil, ether, turpentine, etc., will remove the phenol, not only from the actual surface, but even from the superficial layers of the epidermis and hence cause improvement.

In the same way, these solvents also prevent or delay

the penetration of the phenol, and therefore render it less active, both as to its antiseptic and irritant effects. For this reason a phenol ointment made with a fatty base is very much milder than one made with petrolatum; for the mineral oils are not good solvents of phenol.

Internal Poisoning by Phenol.—Phenol has become one of the most important suicidal poisons, thanks in large part to its pernicious mention in the newspapers. The effects are partly local, reflex, and systemic. There is fairly severe pain, and prompt collapse, with weak pulse, and unconsciousness, coma, and death. The urine has a characteristic dark green (smoky) color, and the amount of free sulphates is much reduced. This is due to the formation of phenolsulphonates. In case of recovery, the local effects are much less severe than with corrosives proper. Stricture is rare.

Treatment of Phenol-poisoning.—The only really efficient treatment is to wash out the stomach with warm water or preferably with alcohol of about 10 per cent., which helps to dissolve the phenol. This washing is naturally most effective the earlier it is done; but since the greater part of the phenol remains for a long time in the stomach, washing should be tried even if the patient is not seen until late.

Of chemical antidotes only syrup of lime and potassium permanganate are of any value; and their efficiency is limited, so that they should be supplemented by emptying the stomach.

Many textbooks still advise the administration of alcohol or sodium sulphate, but it has been shown definitely that these are useless. Their employment was based upon misapprehensions.

Finally, it is necessary to exercise the utmost caution in the sale of this poison, to avoid its suicidal or accidental abuse.

Cresols.—The actions and uses, and the effects and treatment of poisoning by the cresols are practically identical with those of phenol. Their antiseptic action is somewhat more powerful, and their toxicity is no greater. Theoretically therefore they have some advantages; but these are somewhat offset by the more disagreeable odor, and by their limited solubility in water. The last objection may be removed by the addition of soap, as in the official liquor cresolis compositus, or in the proprietary lysol. There are also other ways of increasing the solubility. The alkali adds greatly to the local toxic effects, and renders the cresol preparations more dangerous than those of phenol. Every precaution should be used in their sale.

Creosote and Its Constituent Guaiacol.—These also resemble phenol, chemically and in their actions. They are less toxic, so that they may be employed internally as intestinal antiseptics, and as expectorants in bronchitis. Both of these actions make them useful in tuberculosis. Being irritant to the stomach, they should only be taken on a full stomach. The irritation may be avoided by using the insoluble *guaiacol carbonate,* from which the guaiacol is slowly liberated in the intestine by the action of the pancreatic juice.

Guaiacol is also an active antipyretic. For this purpose it is generally rubbed into the skin.

Salicylic Acid and Its Compounds.—Free salicylic acid is mildly antiseptic, but markedly irritant, and even somewhat caustic. It softens and eventually destroys epithelium. This action is utilized for facilitating the removal of corns (salicylated collodion, etc.). Taken by mouth, the free acid softens the enamel of teeth and produces considerable gastric irritation; its internal use should therefore be avoided; and its use as a food preservative is properly prohibited.

Salicylates as Antipyretics and Analgesics.—The salicylic salts, of which sodium salicylate is the most important, are not antiseptic or irritant. They possess, however, a number of valuable systemic actions. In common with most benzol derivatives, they reduce fever (antipyretic action) and relieve headache and neuralgia (analgesic action). These effects are similar to those of acetanilid and phenacetin, and have no serious advantage.

Salicylates in Rheumatic Fever.—The name "rheumatism" is applied to a variety of joint and muscle pains, and covers a number of entirely different conditions and diseases. In most of these, salicylates are of some value as analgesics; but in one form they are characteristically "specifically" effective. This is the acute rheumatic fever or "acute articular rheumatism." If effective doses of salicylates are used, this extremely painful condition can be completely relieved inside of a day—although this does not remove the most dangerous feature of the disease, namely, the tendency to damage the heart. The effect is produced by all drugs which contain or form the salicyl radical, and by no other drug. In other forms of so-called rheumatism, salicylates are not superior to other analgesics.

To be effective, the salicylate has to be given in large doses, so large as to produce so-called "toxic" effects: ringing in the ears, giddiness, stupidity, nausea, and eventually vomiting. If these effects are carefully watched, very large doses can be given with entire safety.

Sodium salicylate has a disagreeable taste, which is not easily disguised, although most people can take it if it is freely diluted. To prevent the precipitation of the irritant acid in the stomach, it is often mixed with 1 or 2 parts of sodium bicarbonate. If this is still

objectionable, one may substitute the salicylic esters, such as *acetylsalicylic acid* or "*aspirin*," which are nearly insoluble and therefore relatively tasteless, but which are largely decomposed and absorbed in the intestine. *Salicin* also yields salicylic acid in the body.

Acetanilide, Acetphenetidin, Antipyrine.—These and the whole series of so-called "coal-tar antipyretics" belong to the same general group as phenol and salicylic acid. They are somewhat antiseptic, and hemostatic, and may be used as "dusting powders"; but their main practical use is internal: namely, as antipyretics ("against fire") to reduce temperature in fever and as analgesics ("no pain") in headache, neuralgia, rheumatic affections, etc.

Mechanism of Antipyretic Action.—These antipyretics lower the temperature in fever by dilating the blood-vessels of the skin, thus exposing a larger volume of blood to the cooler air. This increased vascularity also favors sweating, and the evaporation of this sweat aids in abstracting heat. Their effects are much more marked in fever than in normal individuals.

Antipyretics are not used as freely as formerly. It is self-evident that they do not reach the cause of the illness, usually a bacterial infection. They merely remove temporarily one of the symptoms. This is no great advantage, unless the rise of temperature is considerable—in which case modern physicians generally prefer to reduce it by tepid baths. Whether baths are theoretically preferable to chemical antipyretics is perhaps an open question. Baths have the advantage that they avoid some undesirable side effects of antipyretics, especially the much-feared *collapse action.* Large doses of the antipyretics tend to cause heart failure. They also alter the blood pigment to *methemoglobin,* and so cause *cyanosis.* The large doses that are required to

reduce fever present some danger of these accidents especially with acetanilid.

Headache Powders.—The much smaller doses which are used for headache and neuralgia—say 3 grains of acetanilid—are not apt to produce these acute effects; but when these doses are repeated at short intervals, they also become dangerous. This is one of the reasons why the proprietary "headache powders," which contain acetanilid, acetphenetidin, and similar substances, are so objectionable. The adjuvants which are present in these powders—caffeine, ammonium carbonate, sodium bicarbonate, etc.—do not diminish the danger; their main object is to disguise the nature of the drug in the attempt to palm off a simple mixture as a new "synthetic," and thus reap a greater pecuniary harvest.

Another danger of these headache powders lies in the fact that they occasionally give rise to an acetanilid or phenacetin habit. This is not so easily acquired as other drug habits, but cases have been reported. The symptoms are similar to those of acute poisoning, namely: cyanosis, cardiac weakness, general debility, etc.

These analgesics therefore should only be used in small doses, which should not be repeated, and it is much safer to leave the responsibility for their use with the physician.

Pine Tar.—This is a complex mixture containing phenol derivatives among other ingredients. It is used particularly in skin diseases as a mild irritant and antiseptic. It is likewise employed in coughs; but it is doubtful whether the quantities present in the syrup of tar do more than flavor the cough-mixture.

Sulphur.—This is used against skin diseases, particularly against itch mites (scabies). It also kills some of the vegetable parasites which are responsible for certain skin diseases. Sulphur, being insoluble, is probably inactive;

but when in contact with proteins, some is converted into sulphides, and probably into sulphites, and the action is due to these soluble products. Sulphurous acid, sodium sulphite, and thiosulphate (misnamed "hyposulphite"), are also used against vegetable skin parasites. We have previously mentioned the use of calcium sulphide. The potassium sulphides ("liver of sulphur") are used for softening the skin and removing hair.

Sulphur undergoes a similar transformation in the intestines, where the products formed give it a cathartic action. The transformation is limited in amount, so that the action is always rather mild, no matter how much is taken. It is more extensive in the finely divided "precipitated sulphur," so that this is not as well suited to the medicinal uses, neither internally nor externally. The "washed" sulphur is the best form.

Mercurials.—All soluble mercury salts are powerful antiseptics; but they are also strongly caustic and toxic, and they have the further disadvantage that they corrode metals, for instance, instruments. They must therefore be used with great care. The most important mercurial antiseptic is mercuric chloride, or corrosive sublimate. This is readily precipitated by organic matter, carbonates, etc. Consequently, it is apt to form turbid solutions with water, unless this is very pure. The precipitation also hinders its penetration into organic materials. The addition of certain substances lessens this tendency to precipitation, and thus renders the mercury less irritant, but also somewhat antiseptic. Sodium or ammonium chloride, hydrochloric acid and citric acid, among others, have this effect, and one or other of these is commonly added, as in the commercial "bichloride tablets." Every precaution should be taken in the sale of these highly dangerous tablets.

Acute Mercury-poisoning.—This is practically confined

to the soluble mercuric salts, of which the corrosive sublimate is the most important. The main symptoms are those of corrosion: burning, pain, dysentery, collapse, coma, convulsions. The tissues touched by the concentrated poison are white and shrivelled, as if cooked. If the patient recovers from the acute effects, these are apt to be followed by nephritis (inflammation of the kidney), colitis (inflammation of the large intestines) and the other phenomena of chronic mercury-poisoning.

The treatment of acute poisoning consists in the administration of precipitants and demulcents. Of these, raw eggs (whole or the whites of six eggs) are the most effective. In their absence one may use milk, flour, or any other demulcent. Sodium hypophosphite has been recommended to reduce the mercuric chloride to calomel. The antidotes must be followed by evacuation, using the stomach tube or ipecac. The patient is given alkalies and plenty of water.

Chronic mercurial poisoning may be produced by either the soluble or insoluble salts. Metallic mercury may also give rise to poisoning, since its fluidity and volatility favor its penetration, even through the intact skin, a fact which is utilized in mercurial treatment by "inunction."

The milder grades of chronic mercury-poisoning are often seen in the energetic medicinal use of the drug in syphilitic conditions. The earliest symptoms usually occur in the mouth, being manifested by a persistent metallic taste, sore gums, and marked salivation ("ptyalism"). These oral (mouth) symptoms are especially apt to occur if the teeth are diseased, or if the mouth is not kept clean. They disappear completely if the drug is withdrawn; but if it be continued, they may go on to ulceration of the jaws and destruction of the teeth.

Diarrhea, from inflammation of the large intestine or

colon, is another early symptom of chronic mercury-poisoning. The kidneys are often damaged.

If the warnings be not heeded, the general nutrition suffers severely, the patient becomes cachectic and nervous derangements set in—tremors, palsy, etc.

Internal Antiseptics.—Bacteria are relatively resistant organisms. Therefore, anything which kills them is very likely also to kill, or at least to injure, the cells of the body. Disinfection, or even antisepsis, in the living body must therefore have a very limited field. In fact, it is confined to a few favorable situations and conditions.

The *skin* is especially favorable, because the stratum corneum protects against the penetration, both of the bacteria and of the antiseptic. *Mucous membranes and open wounds* are less favorable, since they absorb readily. With proper care, however, the injury may be confined to the superficial cells, where it will do little harm, and a limited degree of local antisepsis may thus be secured. In the *alimentary tract,* the danger of systemic absorption and systemic poisoning is a more serious obstacle. This danger can be minimized in certain ways, so that a limited efficiency is possible.

Most bacterial diseases, however, involve the infection of the entire organism. This is true of all the so-called infectious or contagious diseases. In this case, internal antisepsis would be possible only if the invading microbes have a very special susceptibility to some poison, to which the body-cells are relatively resistant. There are a few examples of this, but they are very few indeed, and concern mainly those diseases which are caused by animal microbes (protozoa). The important authenticated examples of such internal disinfection are the following: quinine in malaria; mercury and salvarsan in syphilis; arsenic and certain dyes in some tropical diseases, such as "sleeping sickness," and ethyl-hydroxy-cuprein (op-

tochin) in pneumonia. Such remedies, which strike directly at the specific cause of the disease, are called "specifics." The efficiency of salicylates in rheumatic fever may have a similar explanation, namely, a specific internal disinfection, but there is no definite evidence, since the cause of the disease is not definitely known.

In all other infectious diseases, such as tuberculosis, diphtheria, influenza, etc., etc., the attempts at internal antisepsis have, thus far, uniformly failed; so that it is doubtful whether we shall ever discover specific chemical antiseptics for them. Fortunately, science has achieved better success in another direction, by the use of sera and vaccines, which are to be discussed in a later section.

Ways in Which Bacteria Produce Disease.—Before proceeding further, it will pay to dwell a few moments on the mechanism by which bacteria produce disease. This is generally through the chemical by-products of their metabolism. The alcohol produced in fermentation is a well-known illustration of the production of a toxic substance through the chemical activity of micro-örganisms.

The nature of the toxic substance is peculiar to each organism, and varies greatly. The putrefactive (saprophytic) bacteria, for instance, produce hydrogen sulphide and a variety of ptomains or "putrefactive alkaloids," which are generally organic derivatives of ammonium (amines). These are largely responsible for the toxic actions of spoiled foods ("ptomain-poisoning").

The "pathogenic" bacteria generally produce poisons of a more complex nature, the so-called "toxins." These toxins may be given off to the blood or lymph, as with diphtheria or tetanus. Or they may only be liberated when the bacteria are actually engulfed and digested by the cells (the "endocellular" toxins of typhoid fever, etc.). In either case, they serve the bacteria as a power-

ful weapon in their invasion of the body. For a bacterial infection is not a one-sided process: it is a contest between the bacteria and the cells of the body, in which each needs its most powerful weapons.

The defensive means of the body are several, the most important being phagocytosis and antitoxin formation.

Certain cells of the body have the property of engulfing, killing and digesting bacteria; this process is called *phagocytosis*. The principal phagocytes are the white blood cells (leukocytes or lymphocytes), which are also found in pus, in lymph, in lymph-glands, the spleen, etc. When an infection occurs, these cells are attracted to the infested area to take up their work. Their avidity for bacteria is stimulated by certain chemical substances, of unknown nature, called *opsonins*, which the body produces in response to the presence of the bacteria.

The second protection is furnished by antitoxin formation. These antitoxins act by rendering the toxins harmless. We shall discuss them later.

Intestinal Infections.—Most acute indigestions and diarrheas depend upon the over-development of bacteria and their deleterious products in the alimentary canal. The conditions here are almost ideal for bacterial growth—nutrient material, warmth, alkalinity, and the presence or absence of oxygen in different sections. Oxygen is required by certain bacteria (the aërobic group); it is detrimental to others (the anaërobes).

Accordingly, the intestines normally swarm with bacteria so that half of the bulk of feces consists of them, not of undigested food. Through the course of ages, the race has become so accustomed to these intestinal bacteria that they ordinarily do no harm, and may even aid in digestion. They become deleterious only if cells are for any reason weakened, or if a "pathogenic" (disease-producing) variety is introduced.

The intestines, then, especially the large intestine, contain vast numbers of living bacteria. Under special conditions these may give rise to toxic chemical products such as acids, hydrogen sulphide, ptomains, or toxins, or they may actually penetrate and attack the intestinal tissues. In any case, the intestine reacts by increased movement, or peristalsis, resulting in diarrhea. We have sketched the treatment of this symptom under Astringents. We also touched there on one of the most efficient methods of removing the cause of disease—by cleansing the intestines with a cathartic. Restriction of food is similarly useful by limiting the culture medium. We have also discussed the benefits of chalk and bismuth, which act by neutralizing excessive acidity in the intestine and by binding hydrogen sulphide. On the other hand, the free hydrochloric acid in the stomach acts as an antiseptic, which often prevents the excessive infection of the intestine.

Intestinal Antiseptics.—Cathartics, even when very active, do not empty the intestines completely, and thus they have only a limited efficiency. It would therefore be advantageous to combine them with antiseptics. Not all antiseptics are suitable for this purpose. An intestinal antiseptic must not be easily absorbable; for its absorption would prevent it from reaching the intestine, and it would also present danger of systemic poisoning. The choice would fall on substances which are insoluble in the stomach, but which dissolve slowly in the intestines. This holds true of all the important intestinal antiseptics, such as calomel, salol, and beta-naphthol. Calomel, which is insoluble in water, dissolves in the intestine under the combined influence of the alkali, protein, and sodium chloride. The insoluble salol is decomposed into salicylic acid and phenol by the pancreatic ferments. Naphthol is not changed, but it dissolves so

slowly that its action can extend far into the intestinal tract.

However, many physicians doubt whether any intestinal antiseptics are of much practical value. That they would be seems rather improbable when it is remembered that only a low concentration of the antiseptic can exist in the intestine; and that bacteria are protected by thick layers of feces, fat and mucus.

Gastric putrefaction or abnormal gastric fermentation is best treated by frequently washing the stomach. *Resorcin* is also employed. It is somewhat irritant.

Quinine in Malaria.—The effect of quinine in malaria is one of the best authenticated instances of true internal disinfection. Soon after the discovery of America it was found that large doses of cinchona bark cure malaria or ague. This fact was quite empiric, until it was shown that malaria is produced by the development in the blood of a microbic animal or protozoon, the plasmodium. This is conveyed from patient to patient only by the bite of a particular species of mosquito, in which the plasmodium goes through a certain necessary stage of its growth. The plasmodium, like most protozoa, has a complex cycle of development. The stages through which it passes in the human blood correspond to the phenomena of the disease. The symptoms of malaria consist in febrile attacks, occurring at definite intervals of one to four days, according to the variety of the plasmodium. These attacks are connected with the sporulation.

Quinine is a general protoplasmic poison. It is toxic to all kinds of cells, and even to isolated ferments, but has a specific predilection for ameboid cells; and in this way it injures or kills the plasmodia, without seriously injuring the patient. It is markedly more toxic to the sporulating and free-swimming protozoa. Accordingly, it must be administered in large doses at such a time,

namely, two to four hours before the expected attack, that it will be present in sufficient concentration in the blood at this particular stage of development. In this way it will not prevent the pending attack, but, if effective, it will prevent recurrence.

Other uses of quinine are: as an antipyretic in other fevers and colds; as an analgesic in neuralgia; and as a bitter stomachic and tonic.

High doses of quinine produce "*cinchonism*," disturbance of hearing and sight, delirium, and sometimes nausea. The deafness and blindness are usually only temporary, and serious poisoning is rare, because the absorption is limited by the insolubility of the alkaloid.

Antigonorrheics.—Inflammation of the urethra is treated along the same general lines as inflammation of other mucous membranes. Owing to the very serious complications to which it may lead, especially if it is not thoroughly eradicated, it is very important that its treatment should be undertaken only by a physician. Not only the chronic urethral troubles are attributable to faulty treatment of gonorrhea, but most serious diseases of the wife and most cases of blindness in the children are chargeable to the same cause.

The pharmacist should firmly refuse the temptations which are often put into his way. He should altogether refuse to handle the numerous quack patent medicines which are so much advertised for the pretended cure of this disease. For if they fail to cure—and they generally do fail—the moral responsibility lies with him. It may require some courage to turn down a source of profit, and even more courage to run the risk of offending and turning away a customer. Yet this risk is small in comparison with carrying the load of a wrecked and ruined family on his conscience. Even in a commercial sense the risk is not so very great; for the public prefers a

pharmacist who is conscientious in all that appertains to his profession.

PARASITICIDES AND ANTHELMINTICS

The body is also subject to invasion by larger animals; particularly through the skin and the alimentary canal.

Skin Parasites.—The best preventive, or prophylactic, and the first step in the treatment, consists in cleanliness. The further treatment comprises the local use of substances which are particularly noxious to the unwelcome guests. Among these specific parasiticides may be mentioned:

Sulphur ointment (15 per cent.) against the itch-mite (scabies).

Sodium sulphite and thiosulphate as lotions (10 per cent.) against certain skin diseases due to vegetable parasites ("ring-worm," etc.).

Mercurial ointment (Ung. hydrarg. dil., 3 per cent.) against all animal parasites (its toxic properties must not be forgotten).

Staphisagria or delphinium (10 per cent. ointment or tincture), against pediculi (lice). They cause considerable local irritation.

The phenol group of antiseptics are also used against pediculi.

Anthelmintics.—The intestines are quite frequently the seat of parasites or worms, of which the most important are: tapeworm (Tænia and Bothriocephalus in several varieties); and round-worms (Ascaris). These both occur in the small intestines. Pin- or seat-worms (Oxyuris) occur mainly in the rectum.

Much rarer are the Trichinas, which, however, do not remain in the intestines, but migrate to the muscles, which they irritate and paralyze. Against these there is no cure. The hook-worm (Uncinaria) is of great

importance in the South. It is treated effectively by large doses of thymol or oil of chenopodium.

Domestic animals are frequently affected by similar parasites, although these are usually somewhat different varieties. The tape-worms have a peculiarly interesting life history. The human tape-worm, for instance, does not develop from the egg in man, but these eggs must first be ingested by other animals, the pig or beef, according to species; here the young tape-worm develops in the muscles, forming the so-called "measles," and it is this embryonic form which is capable of infecting man if raw meat is eaten. On the other hand, man forms the intermediate host for the tape-worms of certain of the lower animals. In that case the worm develops in the muscle or other organs of man, being surrounded by a bladder-like "cyst" forming the disease called "echinococcus." If this develops in a vital organ, such as the liver, it may be very serious.

Prophylaxis or Prevention of Intestinal Parasites.—Tape-worm infection, and also that by Trichina, is conveyed mainly by eating insufficiently cooked meat, for the parasites are destroyed by thorough cooking. Ascaris and oxyuris do not require an intermediate host. Their eggs are conveyed directly by contact with excreta, most commonly through sewage-contaminated water, or insufficiently washed uncooked vegetables grown on sewage-contaminated soil.

All intestinal parasites produce innumerable eggs; and prophylaxis must properly begin with the disinfection of the stools of infected patients.

Treatment of Intestinal Parasites.—With the exception of Trichina, these worms are not immediately dangerous to life; but they cause local irritation, digestive disturbance and anemia; and this may become dangerous. Energetic treatment is therefore advisable.

In order to remove and expel these worms from the intestine, they must first be poisoned. There is a large number of drugs or "anthelmintics" ("against worms") more or less efficient for this purpose, and adapted to each parasite.

The parasites, except oxyuris, are so resistant that they require fairly violent poisons—so strong, indeed, that they are not without danger to the patient. "Cures" should therefore not be undertaken until a positive diagnosis has been made. Even then, the vermifuge cannot be given in sufficient amount to kill the worms, but rather to weaken and make it unpleasant for them, so that they can be swept out by cathartics.

Treatment of Pin-worms (Oxyuris).—These are rather delicate, and their situation permits their treatment by enemas. They succumb to almost any mild treatment: soap-suds, salt (½ ounce per pint), quassia (5 per cent. infusion), diluted tr. ferri chlor., etc. Sometimes they have penetrated into the small intestine, and in that case they may require santonin by mouth.

Treatment of Round-worm (Ascaris).—In the treatment of this parasite, santonin has entirely displaced the less reliable remedies which were formerly used, such as spigelia. Chenopodium oil, however, is again coming somewhat into vogue.

Santonin.—This should be given with a little calomel, to aid the expulsion. If the first treatment is not effective, it may be necessary to repeat it.

Santonin causes a peculiar behavior of the urine. This has the ordinary yellow color when passed; but if it turns or is made alkaline, it assumes a pink color. This is due to an unknown decomposition product of santonin.

Excessive doses of santonin produce serious and sometimes fatal poisoning. The symptoms consist in "yellow vision" (all objects assuming a yellowish color),

convulsions, and coma. On account of these serious effects, santonin should be dispensed with care. The popular troches are dangerous, for children may mistake them for candy. They are not needed, for the santonin is practically tasteless, and can therefore be dispensed in powders.

Oil of Chenopodium.—This is an old-fashioned vermifuge against all forms of intestinal parasites. It is quite effective and relatively non-toxic.

Tape-worm Remedies.—The principal are *oleoresin of malefern*, and *tannate of pelletierin.* Both are somewhat dangerous. It is therefore necessary to employ the smallest possible dose; and for this reason the patient has to be prepared by a limited diet, so that the worms will not be protected by fecal matter. At the same time the resistance of the patient must not be weakened by excessive starvation. A purge must be given to expel the worms; calomel and saline cathartics may be used, but never castor oil, since all oils facilitate the absorption and therefore the toxicity of the tenifuges. Pumpkin seeds have had some reputation as a harmless tape-worm remedy; but there is no good evidence that they are effective. At best, they may be employed as adjuvants.

SERA AND VACCINES

Acquired Immunity.—The pathogenic bacteria which produce the infectious diseases poison the body by their toxins. The result may be death or recovery. In many diseases, such as smallpox, measles, whooping cough, etc., one attack of the disease confers lasting immunity. The recovery and immunity are due to the production of specific protective substances ("antibodies") of various kinds. This production is stimulated by the presence of the bacteria.

Side-chain Theory.—According to the famous Ehrlich side-chain theory, the protoplasm contains a large number of chemical side-chains, "*receptors,*" which are essential to the metabolism of the cell. The toxins are supposed to unite with these side chains—directly or by the mediation of secondary substances, "*amboceptors.*" The receptors are thereby thrown out of function. The cell makes an effort to replace these side-chains which are essential to its nutrition. If the quantity of toxin is so great that it binds all the receptors as fast as they can be formed, the cell dies. If, on the other hand, the receptors are formed the faster, it survives. In this case, the cell tends to form an excessive quantity of receptors, as if to protect itself against similar invasions. These spare receptors are given off to the blood, which thereby acquires protective properties. This is an elementary statement of Ehrlich's theory of the production of protective sera. While the theory has not been actually proved, it is currently accepted.

Nature of the "Antibodies."—This differs according to the nature of the bacterial toxin.

Antitoxic Serums.—The bacteria of diphtheria and tetanus form soluble toxins, so that the pure toxins are capable of producing all the toxic effects of the living bacteria. In this case, the protective substances act directly upon the toxin, rendering it harmless, very much as acids are rendered harmless by alkalies. It is therefore said that the antitoxin "neutralizes" the toxin. The injection of such antitoxic serum therefore prevents the effects of the toxin or of the bacteria, provided that the two can be brought into efficient relation. The antitoxin itself has practically no effect upon the patient. Such immunity, conferred by the injection of a protective substance, is called a "*passive immunity.*" It will continue only so long as the antitoxin is present.

Diphtheria and Tetanus Antitoxins.—These are the only antitoxic sera of practical importance. Their injection confers immunity: they protect against infection, and, if given in time, may actually cure the disease. On account of the inaccessibility of the tetanus toxin, this antitoxin has only limited curative value, although it is an effective prophylactic. With the diphtheria antitoxin the curative value is also high. Its introduction has reduced the mortality in this disease from 60 to less than 30 per cent.

Preparation of Antitoxins.—The antitoxins are prepared by injecting horses with increasing doses of the respective toxins. Small quantities of the blood are withdrawn from time to time, and their antitoxic power tested. When it has become sufficiently high, a larger bleeding is made. The blood is allowed to coagulate; the serum is drawn off and preserved by the addition of cresol or a similar antiseptic. This constitutes the antitoxin. The serum is then standardized by determining its protective power on guinea pigs inoculated with definite amounts of diphtheria or tetanus toxins, and comparing this with a standard antitoxin furnished by the United States Public Health Service. This service controls and supervises the manufacture and quality of all similar products, and only firms licensed by the service are permitted to manufacture these sera. The strength is stated in arbitrary units. With diphtheria antitoxin, about 1000 units constitute the immunizing dose; 10,000 units the average curative dose.

The sera may be further refined. The antitoxic qualities adhere to one of the proteins of the serum; and by separating this, a more concentrated preparation is obtained. The serum—crude or purified—may also be dried at a low temperature. The dry sera are more per-

manent. Moist sera must be kept in the ice box, and even so they deteriorate considerably within a year.

Serum Disease.—In many patients the injection of serum, antitoxic or plain, is followed in a week or two by mild symptoms, joint pains, skin eruptions, etc. This "serum disease" disappears spontaneously, and is of no special significance. Much more rarely, there is a serious collapse immediately after injection. This is probably analogous to what is called *anaphylaxis.* Anaphylaxis is a peculiar phenomenon of hypersensitiveness. If an animal is injected with a harmless protein; and then after an interval of a week or two, a second injection of the same protein is made, violent collapse symptoms ensue. The "purification" of the serum has not prevented these phenomena.

Germicidal Sera.—Antitoxic sera act against toxins secreted by bacteria but are without effect on bacteria proper. Another class acts directly on the bacteria of the disease, viz., the germicidal sera. They are practically much less important.

Vaccine Therapy.—When serum therapy was first invented, it aroused the highest hopes, but it was soon found to be restricted. Fortunately there was another way: the production of active, as contrasted with passive, immunity.

All immune therapy starts from spontaneous recovery, which is due to the protective methods of the body. The methods so far described aimed to obtain immune substances from animals; the other method is to make the patient himself manufacture his own immune substances, by inducing a mild and harmless attack of the disease. For this, there are various methods. The oldest is that of *vaccination.* In this, "attenuation" or weakening of the "virus" (the infectious agent) is obtained by passage through a cow; or by a similar disease excited in these

animals. The virus obtained from the sores is marketed mainly as a glycerine emulsion. Vaccination was introduced by Jenner. The immunity against smallpox lasts four to ten years.

Hydrophobia.—A rather similar process is employed in the Pasteur treatment of hydrophobia or rabies. The virus obtained from rabid dogs is inoculated into rabbits. Their spinal cords, which contain the virus, are removed and dried for various lengths of time. This weakens the poison so that it is no longer dangerous. Increasing doses of emulsions of such cords are then injected.

Bacterial Vaccines.—Most generally active immunity is secured by injecting dead bacteria. This is the nature of *tuberculin*, *typhoid vaccine*, etc.

Mechanism of Vaccine Immunity.—The vaccines stimulate the defensive mechanism of the body; but the exact mechanism for this varies. In some cases, the bacteria are killed directly. In others, the white blood-cells are stimulated so that they take up and digest more of the bacteria (phagocytosis). This again is often accomplished by the production of substances, called *opsonins*, which, in some way, render the bacteria more attractive to the phagocytes.

DRUGS USED CHIEFLY FOR THEIR ACTION ON THE ALIMENTARY CANAL

So far we have considered mainly those drugs which are used especially for their local actions outside of the body. We come now to those which are employed for their local effect on the alimentary tract.

The Course of the Food Through the Alimentary Tract.—In the process of mastication, the food is mechanically divided so that it can be more readily acted upon by the digestive juices. At the same time it is intimately

mixed with the *saliva.* This is secreted by three pairs of salivary glands, which are stimulated by the mechanical act of chewing, and by the taste and flavor of the food. The saliva contains several essential constituents: (1) mucus, which lubricates the food mass; (2) an amylolytic ferment or diastase (ptyalin), which converts the insoluble starches into soluble and absorbable sugar (with dextrin as an intermediate product). This ferment acts best in a faintly alkaline medium. This is furnished (3) by the alkaline reaction of the saliva. The sojourn of the food in the mouth is too short, however, to permit extensive digestion. As soon as the food is in proper mechanical condition, it is swallowed. The first portion of this act is voluntary, but when the food reaches the esophagus (gullet), it is passed on by the involuntary contractions of this tube, the cardiac sphincter opens, and the food enters the cardiac pouch of the stomach.

Gastric Digestion.—Even before food reaches the stomach, gastric juice begins to be secreted. This has an acid reaction and contains the protein digesting ferment, *pepsin*, and the milk curdling *rennin.* The acid is necessary for the action of the pepsin. It also makes the gastric juice antiseptic, *i.e.*, it protects the alimentary tract against infection. The gastric juice acts on the surface of the food mass, gradually digesting the protein. The interior of the mass remains alkaline so that the salivary digestive process lasts for a considerable time. The stomach has a further mechanical function: the lower, pyloric end of the stomach, by a series of contraction waves, keeps the food churned, and thus converts it into a fine, smooth mass, the chyme. As this condition is reached, the food is projected, a little at a time, into the first portion of the intestine, the duodenum.

Digestion in Small Intestine.—Here the food meets the alkaline secretions of the intestine. the pancreatic

juice and the bile. These neutralize the acid. This is necessary for the action of their ferments, and also because acidity is irritating to the intestines. The *pancreatic juice* breaks down the proteins into amino-acids; carbohydrates into glucose; and saponifies the fats so that they may be absorbed. The *bile* aids greatly in the digestion of the fats. It is also antiseptic and promotes peristalsis. The *movements of the intestine* are of two kinds. There is a kneading movement, which promotes absorption. The main absorption of the food products occurs in the small intestine. Another stripping movement, peristalsis, propels the contents along. Finally, they reach the *large intestine;* this serves mainly to absorb water, and thus concentrates the fecal matters. The residue is stored in the rectum until defecation.

STOMACHICS AND CARMINATIVES

All the remedies which encourage appetite and stimulate digestion are classed together as *stomachics.* Their number is almost unlimited. They comprise mainly:

Bitters and Aromatics.—These are used in nervous dyspepsia, to stimulate appetite and to increase the flow of gastric juice. The *bitters* act only when taken shortly before meals, probably by enhancing the taste—which is a very important factor in the secretion of gastric juice. A familiar example of a similar phenomenon is the flow of saliva when sour substances are taken into the mouth.

Aromatics also act in a similar manner, but have a further action as mild irritants. This has led to their popular use as *condiments* (pepper, mustard, salt, alcohol, etc.).

Astringent bitters are used especially in catarrhal conditions, since catarrh is generally benefited by astringents.

Carminatives.—The aromatics also stimulate the digestive tract to the expulsion of gas. This is called carminative action, and is especially useful in colic.

Only the type-drugs of these various stomachics need be discussed, since many are practically equivalent.

The Simple Bitters.—These owe their stomachic action solely to their bitter taste. This is generally due to non-poisonous neutral principles and glucosides. *Gentian, calumbo* and *quassia* are the most important members of this group. Small doses of the *bitter alkaloids* are used in the same manner, for instance, strychnine, quinine and hydrastis.

The use of these stomachics, by improving digestion and thereby nutrition, tends to raise the general condition of the patient. They have therefore a "tonic action."

Aromatic Bitters.—These contain both a neutral bitter principle and an aromatic volatile oil. They combine the stomachic action of both classes. *Calamus* and bitter orange peel are examples. Artificial combinations secure the same end, for instance, compound tinctures of gentian, of cinchona, and of cardamon. These have a high percentage of alcohol, which adds to their stomachic effect.

Astringent Bitters.—These contain tannin as well as a bitter principle. Examples are *cinchona, hydrastis, serpentaria,* and *cimicifuga.*

Carminatives.—These contain mainly volatile oils or other "sharp" principles. Those used especially in colic are the *mints, ginger,* and *capsicum. Asafetida* is used especially in hysteria. *Chloroform* and *ether* (Hofmann's anodyne) and *aromatic spirits of ammonia* are also employed.

Sodium bicarbonate is effective in over-acidity of the stomach, while *dilute acids* are given when gastric acidity is deficient.

DIGESTANTS

Most foods must be elaborated by a series of digestive processes before they are absorbed and used by the body. This digestion is accomplished mainly by the ferments which are secreted into the alimentary canal.

Classes of Ferments.—Ferments, catalyzers or enzymes are substances that accelerate chemical reactions without being themselves changed. A small quantity of ferment is therefore able to act upon a large quantity of material. The organic ferments have never been isolated in pure form—the so-called isolated ferments being simply dried extracts, more or less purified. Analogous ferments are found in plants. Some of the digestive ferments are proteolytic, *i.e.*, they act on proteins (the pepsin of the stomach, and the trypsin of the pancreas, and "vegetable pepsin" or papain). Others act on starch and other carbohydrates (the amylolytic ferments or diastases of the saliva (ptyalin), pancreas (amylopsin), malt, moulds, etc.). Others act on fats—the lipolytic ferments (such as the steapsin of the pancreas). Various other ferments are found in nature.

Uses of Digestive Ferments.—The discovery of the ferments raised great expectations of therapeutic usefulness. When digestion does not go on normally, why not give more ferment? or digest food artificially in advance? Unfortunately, the conditions are not so simple; and while ferments are still extensively used, scientific physicians look upon them with much skepticism.

In the first place, indigestion is not usually due to deficiency of ferments, and cannot therefore be benefited by their administration. With pancreatin, there is a further difficulty of getting it to the intestines. The pancreatic ferments are readily destroyed by the acids and pepsin of the gastric juice, and they therefore may

fail to reach the place where they would act. Diastase is also attacked in this way.

For these reasons, it is impossible to prepare permanent mixtures of the ferments in liquid form. The various "compound digestive elixirs" are delusions, practically devoid of digestive action. Considerable proportions of alcohol also destroy the ferments, while glycerine is a good preservative. Excessive heat, of course, destroys all ferments. (The animal ferments act best at body temperature.)

These considerations show that about the only ferment that could be administered with much hope of action is pepsin. However, this ferment plays only a small part in digestion. The acidity of the stomach is much more important than the pepsin.

Predigested Foods.—Since but little can be expected from administration of the ferments, it would naturally occur to one to let them perform their action outside of the body; to use them to predigest the food, and thus spare the stomach this much labor. This also has been rather unsuccessful. The digestive products are not quite the same; and those formed in artificial digestion are rather irritant. In natural digestion, the products never accumulate to the extent where irritation would be produced. For instance, the digestion of fats consists in the liberation of fatty acids. Every one knows how irritant these are in the form of rancid fat; but in natural digestion they are neutralized, absorbed and rendered harmless about as fast as they are liberated.

Practically, therefore, it is not expedient to try to supplant any considerable proportion of natural food by predigested foods. These may, however, have a limited value as an addition to the sick diet. In this, the alcohol and flavors which are commonly added play a considerable part, acting as stimulants.

Pepsin.—This is a dried extract of the pig's stomach. It digests proteins to albumoses and peptones, and is most effective in a moderately acid medium. The activity is easily tested by the official process.

Rennin.—This is a similar, perhaps identical, ferment from the calf's stomach. It curdles milk, and is used for making junket and whey.

Pancreatin.—This is dried pancreas or pancreatic extract. The pancreas contains a number of ferments, of which the following are the most important:

Trypsin.—Digesting proteins more completely than pepsin.

Amylopsin or Diastase.—Digesting starch to dextrin and maltose.

Steapsin or Lipase.—Digesting fats to fatty acids and glycerine.

While all these ferments are supposed to be present in pancreatin, they are so unstable that commercial samples usually contain only variable amounts of diastase; sometimes more or less trypsin; and generally no steapsin.

Pancreatin acts best in a very faintly alkaline medium. It is destroyed by stronger alkalies, by excess of acid, and by acid pepsin.

The main practical use of pancreatin is for "peptonizing" milk.

Papain.—This is a vegetable ferment, digesting proteins in both acid and alkaline media, and acting best in a temperature higher than that of the body. However, commercial preparations are very unreliable.

Diastase.—This is obtained from malt, and from certain moulds. The diastases digest starch to sugar, but since they can act only in an early stage of gastric digestion, their usefulness is very doubtful.

EMETICS AND ANTEMETICS, ANTACIDS AND ACIDS

The stomach is a muscular pouch with tubular openings at the opposite corners, the cardiac at the esophageal end, the pylorus at the intestinal end. These openings are surrounded by muscular rings, the sphincters. The contraction of these ring-muscles keeps the openings closed, relaxing only for the passage of food. This relaxation occurs in response to nervous reflexes, so adjusted that the food will normally pass in the right direction.

Gastric Movements.—After a meal, the bulk of the undigested food is contained in the expanded cardiac pouch, which serves principally for storage, although it permits the digestion of starch by the saliva. A small portion of the food is pushed into the muscular pyloric portion, where it is thoroughly kneaded and mixed with acid gastric juice. When the maceration and digestion of this food mass has reached the proper stage, the pyloric sphincter relaxes momentarily, a part of the mass is pushed into the intestine, the sphincter closes, the pylorus takes up some more food from the cardiac pouch, and the processes recommence. In this way, the stomach empties its contents, little by little, into the intestine. This is the normal course, but when the stomach is irritated, the processes are reversed; the upper (cardiac) opening relaxes; the abdominal walls contract, and food is regurgitated or vomited. This constitutes emesis. The emetic irritation may be produced by indigestion, by irritant food or by poisons.

Local Emetics.—These act by irritating the stomach and pharynx. All irritants may thus produce vomiting, but they are not all adapted to medicinal use; for the irritation must not be so violent as to be injurious. Practically the most important local emetics are:

copper sulphate; zinc sulphate; mustard; ipecac; senega. Tartar emetic is now rarely used, since emetic doses may cause poisoning.

Central Emetics.—These, the second class of emetics, produce vomiting by irritating the center in the medulla which presides over the vomiting reflex. They need not reach the stomach, and can therefore be used hypodermically, whereas all the local emetics must be given by mouth. *Apomorphine* is about the only centrally acting emetic in practical use for this purpose; but emesis by central action is a frequent side effect of other drugs, such as the digitalis group; salicylates, etc.

Nausea.—Vomiting is preceded by the phenomena of nausea or "sickness." With small doses, nausea occurs without actual emesis. The phenomena of nausea consist in a familiar sickening sensation; muscular weakness; increased flow of mucus, saliva, sweat, etc. If the dose is sufficiently small, the increased secretion may be produced without sickness. This degree of action is used to facilitate expectoration in coughing. Nauseants are therefore expectorants.

Antemetics.—Vomiting is also a symptom of many diseases. It is best treated by correcting the underlying condition. If it is due to indigestion, it often serves a useful purpose. However, it may be so excessive as to require direct treatment.

Ice pills are the simplest antemetic.

The insoluble bismuth salts are fairly effective, by allaying irritation. *Cerium oxalate* probably acts similarly; but ordinary doses are too small to be effective, although it is considerably used, especially against the vomiting of pregnancy.

Sodium bicarbonate is often useful. The bitter stomachics, especially strychnine, are sometimes effective; or the sensitiveness of the vomiting center may be dulled

by sedatives, such as bromides, chloral, or morphine. Other cases respond to atropine.

All these remedies often fail, as for instance, in sea-sickness.

Antacids.—The gastric juice as it leaves the glands of the stomach contains about 0.4 per cent. HCl. This acidity is distinctly irritant, and is soon partly neutralized in the stomach to about 0.2 per cent. or less. When this neutralization fails to occur, or when the stomach is hypersensitive to acids, in nervous dyspepsias, the symptoms of hyperacidity or hyperchlorhydria occur—gastric pain or discomfort; acid regurgitation into the mouth, "heart-burn," etc. These are relieved by the administration of alkalies, especially sodium bicarbonate. The proper time for the administration of the alkali is whenever the symptoms call for it.

Acids.—The acidity of the stomach is necessary for the digestive action of the pepsin. It also regulates the sojourn of food and its passage into the intestine; and it acts as an antiseptic. Deficiency in acid is therefore one of the causes of dyspepsia. In such cases the administration of acid is beneficial. The usual doses do not acidulate the entire gastric contents; but they are a material support to the natural acidity. The nature of the acid is not very important. Dilute hydrochloric acid is perhaps the best, although nitrohydrochloric acid is sometimes preferred.

The reaction of the intestines is normally slightly alkaline. Increased acidity produces a cathartic action. Soluble acids are neutralized or absorbed before they reach far into the intestine. An intestinal cathartic effect can therefore be produced only in using difficultly soluble acid salts, such as acid potassium tartrate (cream-of-tartar).

CATHARTICS

To comprehend the usefulness of cathartics, one must recall that the intestinal tract, and particularly the large intestine, swarm with bacteria, which may produce disease, or putrefaction of the undigested food material. The putrefaction is normally kept in check by the elimination of the putrescible material by the feces. But if the putrefaction is excessive, or if the fecal matter is not efficiently expelled, the putrefactive products are absorbed, and give rise to symptoms such as are observed in constipation: indigestion, headache, etc. The accumulation and pressure of the putrefactive gases produces colic, and embarrasses the heart—hence palpitation, irregular pulse, etc. These disturbances are more or less serious, not only of themselves, but because they predispose to other diseases, and render the course of other diseases more serious.

The regulation of the bowels is therefore useful in almost every case of sickness. There are a few well-defined conditions, however, in which cathartics are contraindicated, or where their use requires great caution. The most important contraindications are: all inflammatory conditions of the abdominal organs; pregnancy and menstruation; extreme debility; intestinal hemorrhage; toxic spasm of the intestine.

Cathartics must also be avoided, as much as possible, in *habitual constipation*. This should be treated mainly by diet. The objection to the use of cathartics is, that they keep up a constant irritation, and render the intestine less and less sensitive, so that ever stronger cathartics must be employed. In the end these do serious damage. One should observe the general rule of always employing the mildest cathartic that will accomplish the purpose. All the proprietary and official "liver pills" offend against this rule.

Classification of Cathartics.—The cathartics are so numerous that we can only give a superficial sketch of the most important.

Cathartics are often classified according to the degree of their action:

Aperient, laxative, anticonstipative: single, normal stools.

Cathartic proper: one or several soft stools.

Purgative: several semifluid stools.

Drastic: several fluid stools.

This classification, however, cannot be easily carried through, for the degree of action depends very largely on the dose, although any particular drug is used more often for one degree than for others. It is more useful to follow a pharmacological classification into:

I. Emodin cathartics.
II. Resinous cathartics.
III. Purgative oils.
IV. Mechanical cathartics.
V. Saline cathartics.
VI. Mercurial cathartics.
VII. Sulphur cathartics.

I. Emodin Cathartics.—These contain emodin, chrysophanic acid, and similar derivatives of anthracene.

They act by increasing the sensitiveness of the rectum. The action is comparatively mild, so that they are employed mainly as laxatives and cathartics. Some produce griping, especially senna and aloes. This may be mitigated by the addition of belladonna, or by carminatives (fennel; myrrh). The pure isolated principles are not used in practice (except aloin), since they are irritant in the stomach. In the crude drugs they are protected by the colloidal extractives. The emodins are excreted by the urine, which turns pink on the

addition of alkalies. A similar reaction is given by santonin urine.

The principal members of the group are the following:

Rheum (Chinese Rhubarb).—This has a mild action and an agreeable taste, which make it very useful for children. It also contains a tannin, and therefore produces an after-constipation. It is therefore especially well adapted to the treatment of summer diarrhea, but not so well to habitual constipation.

Cascara Sagrada (Rhamnus Purshiana).—This is mild and effective, and does not produce after-constipation. It is therefore one of the best remedies for habitual constipation. It has a rather bitter taste, which is largely destroyed by boiling with alkalies and corrected by aromatics, as in the aromatic fluid extract. Sometimes the bitter taste is desired for its stomachic effect. The fresh bark is said to contain an emetic principle, which disappears when the bark is stored.

Senna.—This produces a more powerful action and considerable griping. Senna is the principal ingredient of many cathartic "teas," and of the compound licorice powder. The confection of senna is useful for children.

Aloes.—The several commercial varieties act similarly. Their active principles, the aloins, are closely related to the emodins, but are more active. The taste is intensely bitter, so that they must be administered in pill form. Soap and bile are said to increase the activity. Aloes is often used to correct a constipating effect of iron. It produces considerable pelvic congestion and thus increases menstrual flow (emmenagogue action).

Aloin.—This may be used instead of aloes, but it has no special advantage. It is often combined with belladonna (to lessen griping) and with strychnine (which perhaps enhances the action). The "compound laxative pill" also contains a trace of ipecac, which is probably useless.

Phenolphthalein.—This is now used considerably as a laxative. It is tasteless, mild, non-poisonous, and produces only slight irritation and griping, but sometimes irritates the rectum more than cascara.

Phenolsulphonephthalein is injected hypodermically to test the efficiency of the kidneys. Another derivative (*Phenoltetrachlorphthalein*) tests the activity of the liver.

II. Resinous Cathartics.—These contain resinous constituents—i.e., constituents which are soluble in alcohol and insoluble in water. These pharmaceutic "resins" and the eclectic "resinoids" are usually impure mixtures. The cathartic resins are, for the most part, anhydrides of certain organic acids. Their action differs completely from that of the emodins: whereas emodins act mainly on the rectum, with little or no irritation, the cathartic resins produce marked irritation or inflammation of the whole intestinal tract, but especially of the small intestine. This leads to increased secretion of intestinal fluid and violent peristalsis, with frequent liquid stools. Their action is drastic, and since they cause the loss of much water by stools, they are also classed as "hydragogues." The resinous cathartics are therefore not adapted to habitual constipation, but are used as purgatives when prompt and extensive effect is desired. They should be used with caution. Their habitual abuse (for instance, the compound cathartic pills) leads to chronic inflammation of the intestines.

The most important members are:

Jalap.—This produces large watery stools, with relatively little irritation. It is employed in dropsies; often in the form of compound jalap powder, a mixture of jalap and cream of tartar.

Colocynth and Scammony.—These are markedly irritant. Colocynth enters into the compound extract; and this into the compound cathartic pills.

Podophyllum.—This is used exclusively in the form of resina podophylli (podophyllin). The action is relatively mild and slow, but lasts several days. It is therefore often combined with a more rapid cathartic.

Elaterin.—This is one of the most powerful cathartics, but very irritant. It is used as a last resource.

Gamboge.—This is rarely employed.

III. Purgative Oils.—All fixed oils and fats are cathartic, but they act in several different ways.

Croton Oil.—This is a very powerful drastic and hydragogue cathartic, so irritant as to be distinctly dangerous. It should never be used except by physicians. The action resembles that of the resins. It also irritates the skin, and was formerly used as a pustulant.

Castor Oil.—This is perfectly bland, until an irritant fatty acid becomes liberated from it in the intestines.

The action of castor oil is prompt and extensive, with some griping, but little inflammation. It is especially useful when the intestines are to be completely emptied, as in summer diarrhea, or before operations. The intestines are flushed so clean that there is often some after-constipation.

Castor oil should be taken on an empty stomach, since this causes it to pass more promptly into the intestines, avoiding gastric irritation.

Olive Oil.—This acts purely mechanically. When large doses are taken, a part escapes digestion; this "oils" the feces, softening them and lubricating the intestine.

Liquid Petrolatum.—This acts mechanically, precisely like olive oil, but since it is entirely indigestible, much smaller doses suffice, so that it is more readily taken. There is little if any difference in the action of the various petrolatums; but a white and limpid liquid petrolatum is less disagreeable to the taste. The Russian is no

better than the American. The oils are useful in habitual constipation.

IV. Mechanical Cathartics.—Oils and petrolatums may be classed here. Various indigestible gummy substances produce a very similar effect. This applies to *agar* and the various fruits, *cassia fistula*, *tamarind*, *prunes*, etc. The fruits also act by their acid (orange juice); by their indigestible cellulose, which increases the bulk of the feces; and by their content of difficultly digestible sugars. *Manna* belongs in this class.

The action of these mechanical cathartics is very mild; and for this reason, they are well adapted to habitual constipation.

V. Saline Cathartics.—These comprise the magnesium salts, and the sulphate, phosphate, tartrate and citrate of sodium or potassium. They are prompt and effective; and their action can be graded, according to dose, from laxative to profuse hydragogue. Even the severer grades produce little if any irritation. They are therefore adapted to all the uses of cathartics.

The absence of irritation is readily understood from the nature of their action, which is really mechanical. These salts are difficultly absorbed; a portion therefore remains in the intestines; this retains a corresponding quantity of water; and this in turn softens the feces, so that they are more readily expelled. A part, however, of all these salts is absorbed and excreted by the kidneys. This also carries with it a corresponding amount of water, so that the urine flow is increased. The body, therefore, loses water by both channels. This makes the salines very useful in dropsies.

The quantity of salt absorbed is greater when the salts are given in concentrated solution. They should therefore be diluted if a maximum cathartic action is desired. It is also well to give them on an empty stomach

(before breakfast); this will cause the solution to pass more rapidly into the intestines, and the effect is correspondingly more prompt.

There is little to choose between these various salts from the standpoint of efficiency; but the taste of some is much more disagreeable than that of others. Sodium phosphate and Rochelle salt are among the least "bitter." Epsom salt is intermediate; and Glauber salt is about the worst. However, the taste is very much diminished by dilution; flavors are useless.

Mineral Waters.—Sodium or magnesium sulphate are the principal active constituents of cathartic mineral waters. Carlsbad water for instance, consists essentially of sodium sulphate and bicarbonate; Hunyadi mainly of magnesium salts; etc. Sulphur waters contain hydrogen sulphide, which is also cathartic. Other common constituents are sodium chloride, calcium carbonate, small quantities of iron or arsenic, and minute traces of other minerals.

Artificial Mineral Waters.—The natural mineral waters can be effectively replaced by artificial mixtures of their main constituents, contrary to the popular belief. It is often stated that the chemist may determine that a given mineral water contains, for instance, Mg, Na, SO_4 and Cl; but that he cannot determine how these are combined, and that, therefore, he could not imitate a natural mixture. This is untrue: two solutions containing the same quantity of these elements will always contain them combined in the same way, no matter whether they have been introduced as NaCl and $MgSO_4$, or as Na_2SO_4 and $MgCl_2$. When brought into solution, these salts break up into their constituent parts or "ions;" and then remain free or recombine in proportion to the ratio of all the other ions present.

It would not be practical to imitate all the constit-

uents which occur in minute traces in the natural waters. This, however, is not an important matter, for undeterminable traces do not have medicinal effects.

A few of the natural mineral waters are radioactive at the source, but they lose this property soon after bottling.

It can, therefore safely be concluded that the medicinal action of every mineral water is completely represented by an artificial mixture of its principal constituents. The assumed superiority of the natural waters seems to be altogether imaginary. This, of course, does not excuse fraudulent substitution of artificial for natural waters; stealing is not justified by the fact that the victim might be better off without his money.

The undoubtedly superior benefits of a sojourn at the "Springs" are explained by the hygienic and other treatment; and in a few cases by radioactivity.

As a matter of fact, most if not all the natural mineral waters are marketed under exaggerated or even fraudulent claims, at least as to activity. Lithia water is a flagrant example.

Lithium.—Lithium salts were at one time used in "gravel" (urate deposits in urine), gout, and rheumatism, on the theory that they helped to dissolve and eliminate uric acid.

It was found, however, that rheumatism has nothing to do with uric acid; that lithium does not increase the elimination of uric acid; and that it does not even dissolve uric acid in the presence of sodium salts, and that therefore it is inactive in the body. It is true that pure lithium urate is comparatively soluble; but this has no bearing on the question. Lithium salts may be of a little use, since they are somewhat diuretic; but this action is possessed equally by sodium or potassium, while lithium is much more toxic.

However, the lithium question is really not concerned with the lithia waters, for these generally do not contain enough lithium to be entitled to the name. Government investigation showed that the most popular "lithium" water contains no more lithium than does the water of the Potomac River; and that one could not get an effective dose of lithium by drowning himself in the water. Such waters are, of course, absolute frauds.

Glycerine Suppositories.—These secure a prompt stool, by a mild local irritation of the rectal mucous membrane.

Enemas.—These act mainly mechanically, by distending the rectum. *Soap* (which may also be used as a suppository) and *bile* add a mild irritation. *Olive oil* is useful for softening hardened fecal masses.

VI. Mercurial Cathartics.—Mercurial compounds irritate the intestines, as they do all other tissues; and therefore produce diarrhea. The insoluble mercurous salts, especially calomel, and preparations of metallic mercury are the most available. These are converted into soluble compounds in the intestines, but so slowly that the irritation is not harmful. In certain conditions, calomel also increases the flow of urine. The quantity which can be dissolved is limited, so that large doses do not produce much more local action than relatively small doses. In some susceptible individuals, however, even small doses produce rather violent effects. Further, the conditions for solution vary; and if they should happen to be favorable, the large doses may be dangerous. In any case, the continued use leads to an accumulation of mercury in the tissues, and thus to the effects of chronic mercury poisoning—salivation, sore teeth, etc.

The mercurials are, therefore, not adapted to chronic constipation. They are especially useful in intestinal putrefaction, their antiseptic action combining with their cathartic effect, to cleanse the bowels. Intestinal

putrefaction, often due to constipation, produces headache, fever, etc. These were formerly attributed to the retention of bile; and since they are relieved by calomel and similar cathartics, it was supposed that these increase the flow of bile, so that they were classed as "*cholagogues.*" This belief was also fostered by the calomel stools, which have a deep green color, as if they contained bile. However, exact observations have shown that the flow of bile is not increased. The calomel stools may contain more bile, because the antiseptic action and the quick peristalsis prevent the normal destruction of bile in the intestines. However, the dark color of the calomel stools is due mainly to mercurous sulphide.

Jaundice.—Retention of bile is characterized mainly by jaundice (yellow skin) and digestive disturbances. Jaundice or icterus is often benefited by cathartics and alkalies, because these allay the intestinal irritation which, by obstructing the opening of the bile duct, is a frequent cause of jaundice.

VII. Sulphur.—This is quite insoluble, but is converted into soluble sulphides in the intestines, and these stimulate peristalsis. The conversion is slow, so that the stools are only softened, even if large doses are given. This makes sulphur useful in hemorrhoids or piles. Precipitated sulphur, because of its fineness, is more active.

The formation of sulphides also occurs when sulphur is applied to the skin. The ointment is used in scabies (itch).

Time of Action of Cathartics.—This depends on circumstances. Ordinarily, it is about as follows:

Salines, one-half to one hour on empty stomach; two to four hours if in bed.

Castor oil, one to two hours on empty stomach.

Jalap, three hours or less.

Senna, four to five hours.

Rhubarb or phenolphthalein, four to eight hours.

Cascara or aloes, eight to twelve hours.

Podophyllum, ten to sixteen hours.

Toxicology of Drastic Cathartics.—Poisonous doses of the more violent cathartics produce inflammation of the intestines (enteritis), with pain, violent and exhausting diarrhea, etc., as described under irritants. An incidental effect of the inflammation is increase of the menstrual flow, and the induction of abortion.

UTERINE DRUGS AND ANTISPASMODICS

Emmenagogues.—These are drugs which increase the menstrual flow. All irritant cathartics have this effect, since the blood-vessels of the uterus are in nervous connection with those of the intestines, and are dilated when the intestines are irritated. Aloes especially are used in painful or difficult menstruation (dysmenorrhea); they are often combined with iron. This acts as a tonic and thus strikes at one of the main underlying causes of amenorrhea (deficient menstruation). Certain irritant volatile oils, such as pennyroyal, tansy, savin, etc., are used by the laity for the same purpose; mainly as infusions of the herbs.

Abortifacients.—These oils are also employed in a similar manner for procuring abortion; but the large doses necessary for this end are more often fatal than effective. The same holds true of all other abortifacients—or as they are also called "ecbolic" or "oxytocic" drugs.

However, ecbolics also have important legitimate uses in obstetrics.

Ergot.—This is a fungus growing on the grains of rye. Its chemistry was long in dispute, but finally seems to be

cleared up. It is now recognized that it contains a number of active principles differing in their actions. The following are the most important:

Constituents of Ergot.—(*a*) Two alkaloids:

1. *Ergotoxine* (amorphous).—This is responsible for the main actions on the uterus and on the blood-vessels, as also the phenomena of chronic ergot-poisoning. It is a hydrate of the second alkaloid:

2. *Ergotinine* (crystalline).—This is inactive, but changes readily into ergotoxine.

These alkaloids are soluble in alcohol, and sparingly soluble in water; but they are precipitated by acids. They are mainly concerned in the effects of the alcoholic preparations.

(*b*) Several complex aromatic amines, which are also produced in a putrefaction of meat and other proteins. They are soluble in water, and are mainly responsible for the actions of aqueous infusions and extracts. These have received special trade names.

3. *Tyramine* (parahydroxyphenylethylamin).—This constricts blood-vessels and produces a rise in blood-pressure.

4. *Histamine* (beta-iminazolylethylamin).—This lowers blood-pressure, increases peristalsis and contracts the uterus.

5. *Acetyl Choline.*—This lowers blood-pressure and weakens the heart.

Synonyms of Ergot Principles.—Many of these were applied to impure mixtures and are now antiquated. Even these, however, have not altogether disappeared from the literature, and may therefore be quoted for reference:

Cornutine-Kobert = Alkaloidal resin.
Cornutine-Keller = Impure mixture of ergotoxine and ergotinine.
Chrysotoxin = Inert coloring matter with adherent alkaloids.
Ergamine = Histamine.

Ergotamine = Tyramine.
Ergotidine = Histamine.
Ergotine = Sometimes fairly pure ergotinine; sometimes impure mixtures or even crude extract.
Hydroergotinine = Ergotoxine.
Secaline toxin = Mixture of ergotinine and ergotoxine.
Secaline = Impure ergotinine.
Sphacelinic acid = Inert resin with adherent alkaloids.
Sphacelotoxine = Impure ergotoxine.
Uteramine = Tyramine.

Actions of Ergot.—It will be seen from the preceding that the effects of ergot are complex.

Briefly they consist in:

Contraction of the pregnant uterus.

Constriction of vessels with rise of blood-pressure.

Increased movements of the intestines.

Sometimes temporary fall in blood-pressure.

In *chronic ergot-poisoning,* such as occurs from eating bread contaminated with ergot, extensive gangrene occurs, so that entire limbs may die and slough away. Other patients exhibit contractures of muscles.

Therapeutic Uses of Ergot.—Ergot has been used for various purposes, such as to stop intestinal hemorrhage; to raise the blood-pressure; to produce abortion, etc. Its effects in these directions are too inconstant for practical use, so that there remains mainly one legitimate application, but this is very important, viz., to stop hemorrhage of the uterus after childbirth. It does this by contracting the uterus more rapidly, thus closing the bleeding blood-channels.

Deterioration and Assay.—The active principles of ergot, and especially the alkaloids, are unstable. The drug and its preparations deteriorate more or less rapidly, and standardization would therefore be very desirable. The complex chemical composition makes chemical assay out of the question. We must resort to bio-assay,

i.e., determine the efficiency by testing its physiological effects. Several methods have been proposed; but none is entirely satisfactory. The easiest and on the whole the most satisfactory is to administer a certain dose to a rooster. If the drug is active, the comb becomes blackened in a few hours. It is difficult to determine the exact strength in this way; but at least one may know whether the sample is active or inactive. This is much better than to rely simply on the age of the preparation, since the rapidity of the deterioration varies according to conditions.

The Principles of Drug Standardization on Animals ("Bio-assays;" "Physiologic Standardization").—The aim of all drug standardization is to secure therapeutic uniformity. Chemic assay, where it is feasible, is usually the easiest and often the most exact method of standardization. However, there are many drugs for which no reliable chemic method of quantitative assay has been discovered. Indeed, this is hopeless in the case of drugs that owe their activity to the combination of several constituents. These furnish the special field of bio-assay.

Bio-assay is based on the familiar observation that the effects of drugs depend upon the dose. The tissues and organs of an animal react with a drug quantitatively, very much as do chemical reagents in the test-tube. The changes in the physiologic functions of the animal correspond to the "indicators" in a chemical assay.

In other words, bio-assay aims to determine the dose of a drug that is required to produce a given "standard" response on the part of an animal; this dose would then contain the standard quantity of the drug.

In practice, the matter is not quite as simple, because animals are more variable than chemicals, and therefore do not always respond with quantitative accuracy.

This is because the response of living beings depends upon a number of variable conditions, which may vary quite independently of the drug. These disturbing factors can be more or less eliminated, discounted and interpreted by the experience and judgment of the operator. This requires a broader knowledge of biology and medicine than is usually possessed by the pharmacist; and for this reason, bio-assays scarcely belong in his field. It would therefore be superfluous to discuss here the details of the bio-assays; only the principles need be presented.

Cotton Root Bark.—This has been tried as abortifacient, but it is practically ineffective.

Pituitary Extract.—In the skull, just underneath the brain, is a small white gland, the *Pituitary body,* or *hypophysis.* Extracts of the posterior (infundibular) lobe of this gland produce effects which resemble those of ergot. It has a similar tonic action on the uterus, and is used to hasten labor. It secures powerful peristalsis, and is employed as a cathartic after abdominal operations. It also causes a moderate rise of blood-pressure and increase of urine flow but arrests the excessive urine secretion and thirst of diabetes insipidus. The active principles have not been satisfactorily isolated. The extract is used hypodermically; being relatively inactive by mouth.

Official Bio-assay Method for Pituitary.—This determines its effect on the uterus. This organ makes rhythmic contractions if it is placed under suitable conditions, even after its removal from the animal. These movements can be transmitted to a lever, and recorded on a revolving cylinder. These movements are greatly strengthened when pituitary is added to the solution in which the uterus is bathed. The effect is compared with that of a known solution of histamine, a definite chemical substance that produces a uterine effect very

similar to pituitary. The uterus of the guinea pig is used in the official process. Pituitary can also be assayed by its own blood-pressure, but the results of the two methods are not comparable.

Uterine Sedatives.—A number of drugs have been recommended against excessive and painful or suppressed menstruation. *Viburnum* is probably the best known drug of this class; but there are many others scarcely worth mentioning. Exact observations, clinical, as well as experimental, have failed to confirm their reputed value. They are largely sold in the form of "patent medicines" for "female weakness;" but it is very doubtful whether these have any action beyond the psychic effect of the contained alcohol.

Hysteric Sedatives—Antispasmodics.—Hysteria is a peculiar condition of nervous hyperexcitability and perversion, with a great variety of imaginary symptoms. Its treatment requires mainly tact, education, tonics and hygiene. However, a number of remedies seem useful, especially during the attacks, although their action is difficult to judge, because of the impressionable nature of the subjects. It is also worth remembering that hysterical patients are often hypersensitive to drugs.

The principal hysteric sedatives or antispasmodics are: *asafetida, valerian, sumbul* and *musk.* They all possess a marked, generally disagreeable odor. This may be the basis of their action.

Asafetida.—This is usually given as pills. It is also a carminative, and the emulsion is injected as an enema when the intestines are over-distended with gas.

Valerian.—This is used as infusion, tincture, and an ammoniated tincture. Valeric acid and the valerates seem to be ineffective; but several esters of valeric acid appear to be more promising.

TONICS

These may be defined as remedies that cause a gradual and persistent increase in the nutrition, vigor and resistance of the body as a whole. The result can only be accomplished by proper *rest* (including appropriate exercise) and by *nutrition*. Tonic measures are therefore largely non-medicinal, but hygienic and dietetic. Nutrition, however, may be influenced by drugs, which in this way act as tonics.

These comprise, in the first place, measures which put the digestive functions in proper condition: laxatives, stomachics, etc. Strychnine acts as a bitter and improves the muscular tone. Quinine is a bitter, but rather inferior since it hinders somewhat the action of ferments. Alcohol, in moderate doses, is a food and favors rest. Beef extracts aid digestion, but act mostly as stimulants.

Stimulants also increase functions; but their action is short and evanescent, while that of tonics is slow and lasting. Stimulants generally result in the mere expenditure of energy, whereas tonics store up energy.

Iron Preparations.—These act as hematinic tonic, *i.e.*, they restore impoverished blood. They are useful in anemias, whether these are due to hemorrhage or disease, except in one serious condition, pernicious anemia, in which iron is useless.

Importance of Iron.—To understand the effects of iron, we must recall that it is an essential constituent of all protoplasm, but especially of the blood-pigment hemoglobin. It is necessary therefore for the conveyance of oxygen by the blood. The red blood-cells are rather short-lived, and as they die, their hemoglobin is destroyed. This loss must be replaced by the formation of new hemoglobin, and this requires iron. Iron is very abundant in nature; but it is rather slowly ab-

sorbed, and must pass through intermediate forms before it is converted into hemoglobin. To guard against sudden losses, the liver, spleen and bone marrow store an amount as "*reserve iron,*" in a readily convertible form. This reserve iron comes partly from the food, partly from destroyed hemoglobin. It permits a man to recover his blood quite rapidly even after a severe hemorrhage. The administration of iron to normal individuals simply increases this reserve, for the quantity of hemoglobin cannot be increased above the normal level.

Iron in Anemias.—In conditions of anemia the reserve iron becomes inadequate to replace the hemoglobin. This occurs whenever there are extra demands or defective assimilation; as in pregnancy; chlorosis; repeated hemorrhages; exhaustive diseases; intestinal parasites, etc.

These conditions are markedly benefited by the correct administration of iron preparations. The absorption of even small quantities of iron suffices; but the absorption of iron is so imperfect that relatively large doses must be given.

Local Actions.—The large doses, with most iron preparations, tend to produce a local astringent and irritant action, often resulting in disturbed digestion and constipation. These local effects may be useful in some cases, when there is an intestinal catarrh, or excessive formation of hydrogen sulphide; but in most cases, the interference with digestion largely destroys the benefits which would be secured by the iron. One must, therefore, choose the golden mean.

Choice and Administration.—This may be done by skillful management, beginning with the preparations with least local action and gradually accustoming to stronger, at the same time keeping the alimentary tract

in good shape and the bowels open by laxatives. The different iron preparations differ greatly in their local effects. These are least with food iron, and increase progressively with true organic iron, reduced iron, ferrous carbonate, scale salts, ferrous sulphate, soluble ferric salts, the last being most irritant.

Hence, a considerable number of iron preparations are really needed, although the official list could be profitably reduced.

Where graduated administration is not feasible, Blaud's pill and the saccharated carbonate are the best all-around forms.

To avoid gastric irritation, all forms of iron should be taken on a full stomach. Combinations with bitters are therefore not ideal, since these must be taken before a meal. The only exception is reduced iron. This should be given shortly before meals, so that it may be dissolved by the gastric juice. Soluble iron preparations injure the teeth. Ferric chloride is especially detrimental. The mouth should therefore be rinsed with lime-water. The constipating action of iron may be corrected by aloes or other laxatives. The use of iron as a styptic has already been discussed.

Arsenic.—The arsenic compounds act as tonics, alteratives, and parasiticides. *Alteratives* influence abnormal tissue change, while tonics act equally on normal metabolism.

Tonic Action of Arsenic.—Therapeutic doses increase the permeability of the blood capillaries, so that the exchange between blood and tissues is favored. This results in improved nutrition. Arsenic is therefore useful in anemias; in all kinds of wasting diseases, marasmus and cachexia; in delayed growth, especially of the bones; and in many skin diseases. Its popular use to whiten the complexion has often caused chronic poisoning.

Administration.—Internally, the arsenic is usually administered as Fowler's solution, beginning with a small dose and increasing to the limit of tolerance. This is indicated by puffy eyelids and digestive distrubances. The dose must be greatly reduced when these appear.

Locally, arsenic trioxide is a mild and slow caustic. It enters into many "cancer-salves," but its use is too dangerous.

Toxicology of Arsenic.—Arsenic is one of the most popular of poisons, because of its innocent appearance and taste, and the ease with which it can be secured. Acute poisoning, accidental as well as criminal, is quite common. Chronic poisoning is produced by the presence of arsenic in wall-paper, dyed fabrics, etc., etc.

Symptoms of Acute Arsenic-poisoning.—These consist in vomiting with violent diarrhea, the stools resembling rice-water. The patient gradually passes into collapse. These effects are not due to direct local irritation, but to the systemic action on the capillaries.

Treatment.—The stomach should be emptied and washed with warm water. Milk, raw eggs and magnesia help to delay absorption. The official "arsenic antidote" (ferric hydroxide with magnesia) is probably not very efficient.

Symptoms of Chronic Arsenic-poisoning.—These consist of digestive disturbances; puffy eyelids; albuminous urine; a peculiar pallor of the skin; and often skin eruptions and nervous derangements.

Organic Arsenic Compounds.—Metals generally produce their typical effects only when they act as easily dissociable salts; not when they occur as firm organic combinations. In the body, however, the organic compounds are slowly broken down and then cause the typical effects. The organic combinations are therefore much less toxic, and act much more gradually. Further, these

combinations often secure effects which differ, in degree and even in kind, from those of the simpler compounds. They therefore have distinct uses.

The organic arsenic compounds are of two types, one containing pentavalent, the other trivalent, arsenic. Their structures are illustrated by the formulas:

Pentavalent

Arsenic acid:

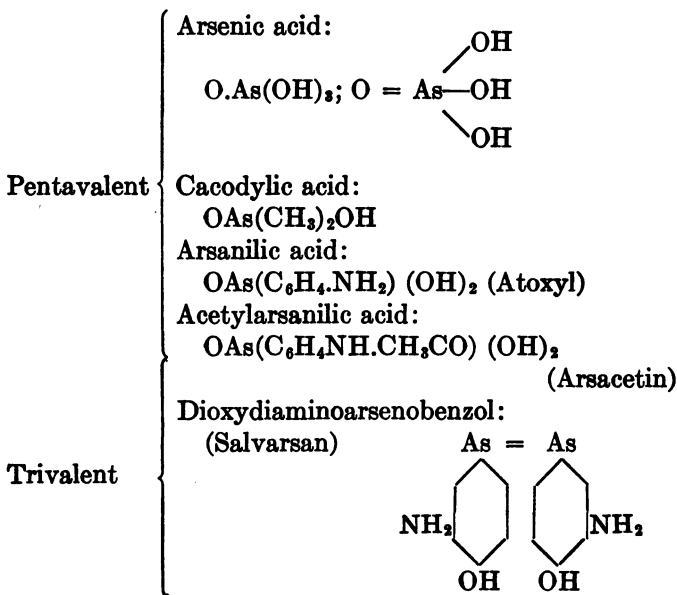
$O.As(OH)_3$; $O = As(-OH)_3$

Cacodylic acid:
$OAs(CH_3)_2OH$

Arsanilic acid:
$OAs(C_6H_4.NH_2)\ (OH)_2$ (Atoxyl)

Acetylarsanilic acid:
$OAs(C_6H_4NH.CH_3CO)\ (OH)_2$ (Arsacetin)

Trivalent

Dioxydiaminoarsenobenzol:
(Salvarsan) As = As, each As attached to a benzene ring bearing NH_2 and OH

Sodium Cacodylate.—This has practically the same systemic action as ordinary arsenic; but since it is only slowly decomposed, it acts more mildly, and is sometimes tolerated when the ordinary arsenicals produce too much digestive disturbance. It is used especially in anemias, being usually administered hypodermically. It imparts a pronounced garlic odor to the breath.

Atoxyl and Arsacetin.—These have been found especially effective in a certain tropical disease (sleeping sickness). This is caused by microscopic parasites

(trypanosomes) in the blood. These parasites are killed by atoxyl, so that the disease is cured. Unfortunately, the large doses which are needed sometimes produce permanent blindness.

Salvarsan.—The discovery of this remedy, which is highly effective against syphilis, was not accidental, but the result of well-planned researches in chemotherapy. *Chemotherapy* purposes the cure of parasitic diseases by chemic agents. Syphilis is caused by microscopic parasites, the spirochetes or treponemas. Ehrlich found that these could be killed by trivalent arsenic compounds, but not by pentavalent, until these had been reduced in the body to trivalent. With the ordinary arsenic compounds, the effective dose would be fatal to the patient. Ehrlich therefore sought for some compound which would be more toxic to the parasite, and less toxic to the patient. This systematic search resulted in the discovery of salvarsan and neosalvarsan, the latter being, practically, merely a soluble preparation of salvarsan.

These compounds are very unstable, and their decomposition products are very toxic. They cannot therefore be given by mouth, but must be injected into the muscles or better into a vein. When properly used, they arrest the disease, especially in its early stages. A single injection, however, does not cure the disease, but this recurs sooner or later. The injections must therefore be repeated at intervals, being used in alternation with injections of mercury. In this way, it is possible to produce an absolute cure of this dreadful disease, provided that the treatment is started early and carried through energetically and persistently. The older methods of mercurial treatment very rarely resulted in cure, and would now be little short of criminal.

In the later stages of syphilis, in locomotor ataxia, etc., arsenic and mercury do relatively little good. At

this stage, large doses of iodides give relief from the effects of the syphilis, but they also fail to cure.

Phosphorus and Its Compounds.—Phosphorus is a very important constituent of the body. Phosphates occur in the blood and in all the tissues, and make up the bulk of bones. More complex compounds, lecithin, etc., form an important part of all cells and especially of the nervous tissue. The latter particularly has caused phosphorus to be exploited as a "nerve food," in all forms of nervous weakness and malnutrition, phthisis, sexual impotence, etc.; and every variety of phosphorus, from the element through all its compounds to lecithin, has in turn been praised.

A very little thought shows the absurdity of these contentions. The prevalence of phosphorus in animal and vegetable tissues insures that the ordinary food contains as much phosphorus, in every variety of combination as the body can possibly use. Nor has the slightest deficiency of phosphorus been discovered in the body or any of its tissues in any of these diseases. To administer the ordinary doses of phosphorus with the idea of nourishing the nerve tissue, has about as much sense as to take water in 5-drop doses with a similar object, for nervous tissue contains considerable more water than it does phosphorus.

There is, however, one rational use for elementary phosphorus, and that is for stimulating the growth of bone in rickets. This is a strictly pharmacologic action, not a food effect.

Phosphorus-poisoning.—This is generally due to matches prepared from yellow phosphorus, the red phosphorus being non-toxic. It produces a very peculiar train of symptoms. The immediate effects are those of moderately severe irritation with pain and vomiting, the latter smelling of phosphorus, and being luminous in the

dark. These effects generally pass off in a day, and the patient improves and may seem perfectly recovered for several days. At the end of this time, however, vomiting and diarrhea commence again; intense jaundice develops; the liver becomes enlarged and painful; there are characteristic changes in the composition of the urine; and the condition now ends in profound prostration and death. The liver and other organs are found to have undergone marked fatty degeneration.

Treatment.—This is effective only when started early. The best antidote is copper sulphate, which acts as an emetic, as an oxidizing agent, and which forms a coating of metallic copper around the phosphorus globules. Other oxidizing agents may be used in emergencies: hydrogen peroxide, potassium permanganate. Oxidized phosphorus is not toxic. Oil of turpentine is sometimes effective, but often fails. It forms complex compounds with phosphorus, depending upon the variety of the turpentine. The ozonized is not necessarily superior. Fat must not be administered.

Cod-liver Oil.—Like all fats, this has a high food value; but it appears to favor nutrition and growth even more than other fats. This is due partly to its easy emulsification, digestion and assimilation; partly to the presence of an unusually large quantity of a growth-promoting fatty constituent.

There is no evidence that any of the therapeutic action is due to the putrefactive alkaloids, other extractives, and traces of iodine which are present in cod-liver oil. The "fat-free" preparations therefore seem to be without any value.

Cod-liver oil is useful as a medicinal food, particularly because the patient can often be persuaded to take additional food in the disguise of medicine. Its main use has been in the treatment of tuberculosis, in which ample

nutrition is one of the main factors. It is also used extensively in rickets.

ALTERATIVES

These were supposed to alter abnormal nutrition and chemical tissue change, and to reduce them to normal. They would, therefore, be indicated in conditions of malnutrition. Such conditions were at one time attributed to "bad blood," which is no longer accepted in this sense by medical science. The "bad blood" generally meant indigestion and constipation, and many of the older "blood-purifiers" were largely nondescript mixtures of bitters and purgatives.

The active ingredients are now classified where they belong, while the nondescripts are generally discarded, such as burdock, sassafras, etc. *Sarsaparilla* is used in the compound syrup only as a flavoring vehicle. *Guaiac*, another old time "blood-purifier," which was used in rheumatism and gout, is now classed as a cathartic and little used. The alkalies, sodium bicarbonate, and the salts of organic acids, which are converted into carbonates in the blood, are also used in rheumatism. Another drug which might be classed as alterative in gout is *colchicum*, but there is much diversity of opinion as to the manner of its action, and even as to its efficiency. It is a rather dangerous drug. Excessive doses produce violent vomiting and purging.

It will be seen that the number of alteratives of acknowledged value has greatly diminished. In fact, the term may be restricted to arsenic, mercury, iodides, and thyroid preparations.

Mercury.—This has already been discussed under several headings: mercuric chloride, under corrosives and antiseptics; calomel, under cathartics; ointment,

under parasiticides, etc. We may therefore confine ourselves to its use in syphilis.

Mercury in Syphilis.—One of the most important uses of mercury is in the treatment of syphilis. The mercury administration, if sufficiently energetic and prolonged, destroys the spirochetes to which the disease is due, and therefore effects a cure. Success, however, demands expert supervision and careful control of the progress of the disease by the modern laboratory methods (spirochete examinations, Wassermann tests, etc.). Careless use will not be of any benefit, and may do serious harm. Even with expert administration, and when combined with salvarsan, the treatment must be carried on for several years.

Administration.—The use of mercury by mouth is rather unsatisfactory, since the energetic treatment causes too much digestive discomfort. However, it is still often employed, generally in the form of the protoiodide.

Inunctions.—These are fairly effective, but so disagreeable that it is difficult to secure their conscientious employment.

Intramuscular Injections.—These form the preferred modern method: They employ soluble mercuric salts (HgI_2 plus KI) daily; or more commonly insoluble preparations (calomel, gray oil, mercuric salicylate) weekly. The mercurial treatment is often combined with salvarsan. The injections are made in courses of six weeks with intermissions of about equal length, until the Wassermann reaction becomes permanently negative.

Iodides.—The toxicology of iodides and the phenomena of iodism were discussed previously. The iodides are especially useful in the late syphilitic conditions when they lead to the absorption of the abnormal fibrous tissue, which is a prominent feature of the disease. They

do not kill the parasites, and the mechanism of their action is not definitely understood. They are also useful in aneurism, arteriosclerosis and other fibrous degenerations. Like most salts, they are diuretic and expectorant, useful in bronchitis and asthma. They are often given in chronic rheumatism. They are very effective in certain forms of goiter, but very dangerous in others, so that they should be employed only under medical supervision.

The choice of the iodine compound is of little importance, notwithstanding the claims of manufacturers, that *their* products are more efficient and do not produce iodism. Iodine compounds appear to be effective only in so far as they are broken up into ordinary iodide, and then they produce iodism just as does ordinary iodide. If they do not produce iodism, it means simply that the dosage is not sufficient. Potassium iodide accomplishes everything as conveniently and perhaps more effectively than any other. It is best administered in milk. It is not absorbed efficiently by the skin; hence the ointment of potassium iodide is unscientific.

Thyroid Glands.—These are situated in the neck, being the structures which are enlarged in "goiter." Serious results follow their operative removal or congenital deficiency or disease, as in some varieties of goiter. These effects can be removed by the administration, by mouth, of dried thyroid gland or extract, or its iodine-containing constituent. The administration must, of course, be continuous, since it must supply a continued deficiency in the "internal secretion" of the gland. On the other hand, overdoses are toxic, producing palpitation and rapid heart, nervousness, loss of weight, and collapse. It must, therefore, be used only under supervision. The loss in weight has prompted its use in obesity "cures." It increases tissue destruction, and is

often successful, but usually only temporarily. It is far too dangerous, especially if there is any sign of the thyroid disease "exophthalmic goiter."

EXPECTORANTS

These introduce the drugs that are used mainly in diseases of the respiratory system. The expectorants are so called since they modify expectoration. Some increase its amount, others render it more fluid, and others again diminish its quantity.

Treatment of Coughs.—Expectorants are used in cough and bronchitis. Cough is a reflex, *i.e.*, an involuntary act, which is intended to remove foreign and irritant substances from air passages. Inflammation of the mueous membrane of the bronchi, "bronchitis" or "cold in the chest," like the inflammation of all mucous membranes, is accompanied by increased secretion of mucus. The accumulation of this mucus would obstruct breathing. The obstruction is removed by coughing, which therefore serves a useful end, and must be encouraged if deficient.

The cough reflex, however, may easily be excessive, for it is also evoked by simple irritation; it is then merely annoying or exhausting, and needs to be checked.

Again, the flow of mucus allays irritation; in early stages of bronchitis, before the mucus secretion has set in, the irritation is much more severe, and at this time the principal object of treatment is to establish this secretion.

The treatment of cough is therefore not as simple as is commonly supposed, but must vary according to conditions. It is easy enough to suppress the symptoms; but unless this is done intelligently, it may do more harm than good.

Bronchitis tends to pass through several well-defined stages:

(*a*) In the beginning, the inflammation is acute, but the mucus is scanty, thick and irritant. This requires increase and liquefaction of the mucus, as by so-called *sedative, nauseant, alkaline* and *saline expectorants.*

(*b*) Later on, the secretion is over-abundant, and tends to flood the air passages. This requires remedies which diminish the secretion and stimulate its expulsion, as in the so-called *stimulant expectorants.*

(*c*) Finally, the secretion, again becomes scanty, but the passages remain irritated, leading to a dry but ineffective cough. This requires *demulcents* and *anodyne expectorants.*

Demulcents are useful during all stages to lessen inflammation.

If the larynx is mainly affected, astringents and demulcents may be administered as lozenges.

Sedative Expectorants.—These are used to liquefy the mucus, especially in the earliest stages of cough. They comprise mainly the *nauseants.* Nausea increases all the secretions, among them the sweat, saliva and mucus. When nausea is marked, there is also sickness, disturbed digestion, weakness, fast pulse, etc. The therapeutic dose should be sufficiently small to avoid these undesirable side actions, and to act only on the secretions.

Every emetic causes nausea, but in practice those are preferred whose nauseant and emetic doses lie far apart. These comprise mainly *ipecac* and *tartar emetic.* Ipecac is most useful, tartar emetic being too depressant and somewhat dangerous.

Ipecac.—This contains three alkaloids, of which emetine and cephaëline are the most important. They act essentially alike, and produce the characteristic

effects of the drug. There is also a pseudo-tannin (ipecacuanhic acid) which colors with iron, but is not astringent.

Ipecac is a valuable emetic and nauseant, the action being due mainly to local irritation of the mucous membrane; so that, if simply a nauseant effect is desired, it may be used as a gargle. Since nausea also produces sweating, ipecac is used in the diaphoretic Dover's powder. Very small doses cause a mild stimulation of the stomach, which is useful in certain forms of dyspepsia.

Very large doses, on the other hand, have been found beneficial in "*amebic dysentery,*" presumably by killing the parasites. To avoid vomiting, these large doses must be given in pills coated with a heavy layer of salol. These large doses also irritate the intestine, producing diarrhea. At present, emetine hydrochloride is largely used hypodermically, being more effective and less disturbing to digestion.

Antimony.—This is used mainly in the form of tartar emetic. Its action is allied to that of arsenic; but being much less readily absorbed, it is better adapted for producing local irritant effects. It is employed as nauseant and emetic. It has gone out of favor, since it produces considerable depression; and if long continued, it may give rise to the phenomena analogous to chronic arsenic-poisoning. It is perhaps most useful in small doses as adjuvant to other expectorants, as in the mist. glycyrrhizæ co., and the syr. scillæ co.

The difficultly soluble antimony sulphide irritates the intestines, and produces a *cathartic action.* Applied to the skin as *ointment,* tartar emetic acts as a *pustulant.* The *antimony chloride* or "butter of antimony" is a *cauterizant.*

Alkaline and Saline Expectorants.—Mucus is precipitated by acids and liquefied by alkalies. When therefore the mucus is thick and adherent, and the cough is

for this reason ineffective and excessive, it is advisable to administer alkalies as gargles or sprays. *Sodium bicarbonate* or *borate* may be used in about 3 per cent. solution. For internal use the *ammonium salts* are preferred since they are re-excreted by the bronchi. Ammonium carbonate is the most effective; but the chloride is generally preferred since its taste is less disagreeable. It may also be inhaled by mixing the vapors of HCl and NH_3. *Potassium iodide* also dissolves mucus. It is used especially in chronic coughs. *Potassium bromide* may also be useful in coughs, but it acts quite differently, viz., by lowering the cough reflex.

Stimulating Expectorants.—These are employed, especially in chronic bronchitis, to lessen the secretion of mucus; to promote its expulsion; and to stimulate the mucous membrane to repair. Probably the most effective is *terpine hydrate*, and the related *terebene* and *turpentine*, the latter given internally or by inhalation. For inhaling, however, oil of pine or eucalyptus are more agreeable. The *balsams* of *Tolu* and *Peru* and *storax* and *tar* are also used, as stimulating expectorants; but the doses generally employed have little effect except to flavor. *Creosote* is more effective.

All of these agents are also antiseptic, and are often used in the bronchitis which accompanies tuberculosis. However, they have not the slightest curative effect on the tuberculous process itself.

Anodyne Expectorants.—While the secretion remains abundant and must be removed, it would be inadvisable to stop the cough. However, when the quantity is under control, irritation may still persist, giving rise to a "dry cough." Central sedatives or anodynes may then be used, especially at night, to secure sleep. These arrest the cough, but it must be remembered that they do not cure the bronchitis, they may simply hide the damage.

Prominent among the anodyne expectorants are the opiates: morphine, codeine, heroine and dionine. They are about equally efficient, but codeine is probably the best, since it has the least tendency to habit-formation; while heroine is the worst in this respect and has no compensating advantage. The opiates tend to "dry up" the secretion, since they lessen its expectoration.

Bromides and chloroform are also sometimes used as anodyne expectorants. Hydrocyanic acid, as in wild cherry, has a similar but feeble action.

Demulcent Expectorants.—The soothing effect of demulcents on inflammations has been previously discussed. They are employed in the form of *acacia*, *glycerine*, *syrups*, and especially *glycyrrhiza*. The "*breast-teas*" also depend mainly on demulcent herbs. The demulcents are perhaps best administered as troches, since these give a longer local action.

Cough Mixtures.—What has been said of expectorants will have made plain the place of "cough mixtures" in intelligent therapeutics. They may be effective, and even useful, for *temporary* relief; but they do not, as a rule, help the cure, and may even do damage; while intelligent treatment does both—gives relief and helps in curing. The popular cough mixtures are dangerous, especially in delaying proper treatment. This danger is greatest in tuberculosis, in which the possibility of success depends on early tonic and hygienic treatment. Most cough "cures" depend for their efficiency on opiates, and these may lead to the formation of the dreadful drug habit.

RESPIRATORY STIMULANTS AND ASPHYXIANTS

Respiration is an involuntary function, which renews the air in the lungs, removes the carbonic acid of the

blood, and supplies the oxygen to the body. It is effected by a sort of bellows-movement, through contraction of the diaphragm and of the costal (rib) muscles. These movements depend on a nervous center in the medulla oblongata, the *respiratory center*. This center becomes depressed in pneumonia, collapse, poisoning, etc. The respiration, which is weakened by this depression, may be stimulated by drugs which act directly or reflexly on the center.

Direct respiratory stimulants are: caffeine, atropine, ammonium salts, hydrocyanic acid, strychnine, etc. *Reflex respiratory stimulation* may be produced by "counterirritation;" particularly by the inhalation of weak ammonia vapor (aromatic spts. ammonia) or aromatic vinegar; by mustard baths, etc.

Hydrocyanic Acid and Cyanides.—We may take this occasion to dispose of the subject of cyanides. Hydrocyanic acid is used to some extent in coughs; and as a local analgesic in indigestion; etc. However, its use is restricted, since its action is too fleeting, uncertain and dangerous.

Cyanide-poisoning.—The main importance of hydrocyanic acid and potassium cyanides lies in their poisonous action.

They are generally considered as among the most fatal poisons. This does not mean that they are the strongest poisons, for there are many others which kill in much smaller doses; but the course of the poisoning is so rapid, death often occurring within five minutes, that there is little chance for treatment, and the fatality is thus very high.

The *symptoms* consist in collapse, unconsciousness, convulsions, arrest of respiration, and death. These symptoms resemble asphyxia; and indeed, the effects are due to interference with the ferments that bring about oxidation in the tissues.

The *treatment* is not very successful, unless it is applied immediately. A number of chemical antidotes have been advised, the "arsenic antidote" (ferri hydroxidum cum magnesii oxido); sodium thiosulphate ("hyposulphite"); permanganate; hydrogen peroxide, etc.; but the absorption is so rapid that there is little chance of success. Evacuation, however, should be tried. The collapse symptoms should be treated by stimulants, ammonia, etc. Artificial respiration should also be tried. Ferrocyanides, ferricyanides and sulphocyanides do not produce the effects of simple cyanides, and are relatively non-toxic.

ASPHYXIANT AND TOXIC GASES

The symptoms of cyanide-poisoning are really those of a rapid asphyxia. Very nearly the same effects are produced by the poisonous gases, such as CO_2, CO, H_2S and some others.

Hydrogen Sulphide.—This is highly toxic and when inhaled in concentrated form, it kills almost as rapidly as hydrocyanic acid.

Carbon Dioxide (Carbonic Acid).—This is not nearly so poisonous; a fairly high concentration is required to kill. The noxious character of "impure air" is not due to CO_2, but apparently mainly to the heat and moisture, and to disagreeable odors.

Carbon Monoxide.—This is very important, being the main toxic agent of artificial coal gas, and also of the fumes of incomplete combustion. It combines with the hemoglobin of the blood, and thus prevents it from carrying oxygen. Under ordinary conditions, *i.e.*, when gas escapes or is formed slowly, the asphyxial symptoms develop gradually, with drowsiness, passing into unconsciousness. Convulsions may appear later. The pupils

of the eye are widely dilated, as in all asphyxias. The veins are congested. The color of the skin, however, is not the dusky blue of ordinary asphyxia, but a cherry-red, corresponding to the color of CO, hemoglobin.

The *treatment of asphyxias*, consists in artificial respiration and the administration of oxygen.

Oxygen.—The proportion of oxygen present in ordinary air (about 20 per cent. by volume) is more than sufficient practically to saturate the hemoglobin of the blood. The inhalation of pure oxygen therefore produces little if any effect in normal individuals. However, in asphyxial conditions, when the air cannot readily reach the lungs; when the respiration is depressed; when toxic gases have been inhaled; when the lungs are blocked by pneumonia, etc., the inhalation of oxygen relieves the deficiency and thus removes the asphyxial symptoms. The oxygen gas is administered by bubbling it through a wash-bottle with warm water, from which it passes through a tube into a funnel, suspended over the face so as to saturate the air about the mouth and nose.

Asthma.—This consists in recurring attacks of difficult respiration and asphyxia. There are several varieties, due to different causes. The most common is a spasmodic contraction of the muscles of the small air tubes or bronchioles. The attack would therefore be relieved by paralyzing these muscles. This is done most effectually by *epinephrin;* and by *atropine* and drugs containing it, *belladonna* and *stramonium*. *Lobelia*, *conium* and *tobacco* have a similar action. To bring these into the bronchi most directly, they are generally administered by inhaling the smoke of the leaves burnt with saltpeter. Burning paper alone, in the form of charta potas. nitratis, has a similar effect. Epinephrin is always used hypodermically.

At the same time the respiratory distress may be

allayed by morphine. It presents the grave danger of habit-formation; and should not be used except by the physician.

Atropine and morphine are similarly useful in various *colics*—intestinal, gall-stone, or kidney-stone.

DRUGS THAT ACT ON THE CIRCULATION

To understand these, we must review the physiology and pathology of the heart.

Physiology of the Circulation.—The blood serves to bring to the tissues oxygen and nutriment, and to remove CO_2 and other waste products. It must therefore be in circulation. Even a short arrest results in death. The blood is kept moving by the contractions of the heart, which acts as a force pump. It is directed into the proper channels by the valves of the heart.

Blood-pressure.—The contractions of the heart acting against the friction or resistance of the blood-vessels produce a certain pressure, the blood-pressure, which decreases from the arteries through the capillaries, to the veins, where it may be negative. By "blood-pressure," is ordinarily meant the arterial blood-pressure.

This is a resultant of two factors: the output of the heart and the resistance of the vessels. The blood-pressure will be raised by increased rate or force of the heart within certain limits, and especially by contraction of the arterioles. It will be lowered by slowing or weakening the heart, or by dilating the vessels.

Nerves of the Blood-vessels.—The caliber of the vessels is controlled by nerves, some of which cause the vessels to constrict, others to dilate. These nerves are under the control of the nervous center in the medulla oblongata, the "vasomotor center." This center is called into action by various reflexes. The caliber of the vessels may therefore be altered by drugs acting on the vessels

themselves; or on the vasomotor center; or on the reflexes.

Nerves of the Heart.—The heart can contract without nerves; but its rate is modified by certain nerves, viz., slowed by the *vagus*, and quickened by the *accelerators*. These also have their centers in the medulla which may be affected by drugs directly or reflexly; or the nerves may be stimulated or paralyzed by drugs in the heart itself. In man, and most mammals, the heart is constantly under partial restraint by the vagus; so that it may be quickened, either by paralyzing the vagi or by stimulating the accelerators.

The Pathology of the Heart.—Disturbances of the heart may be anatomic or functional; that is, with or without structural changes.

Valvular Diseases.—By "heart disease" is generally meant anatomical changes in the valves. These are altered by disease, generally as a result of their infection, particularly after acute rheumatism. Such infections may deform the valves so that they close incompletely and leak (incompetency); or so as to narrow their orifice (stenosis).

Consequences of Valvular Defects.—In either case, there is interference with the propulsion of the blood in the proper direction. Less blood is propelled into the arteries, and important organs are therefore imperfectly nourished. On the other hand, the blood is dammed back on the venous side of the heart, on the lungs and on the right heart. This means that the blood is not properly oxygenated in the lungs. The patient is therefore dyspneic ("short of breath"), and cyanosed (dusky color). The damming back also dilates the heart and causes it to become irregular and still more ineffective. The congestion of the veins finally allows the plasma to filter through the vessels, as it were, and thus causes

dropsies. The back-pressure and defective arterial pressure interfere with the functions of the kidneys, and these favor the dropsy.

Compensation.—In favorable cases, the heart muscle grows up to the demands which are made on it, by *hypertrophy*. It "compensates" for the lesion. Patients with "compensated lesions" are to all intents normal, unless they make some excessive demand on the heart. But the margin of safety is narrow, and any exertion or excitement may bring on incompensation, with the effects which have just been described. Sooner or later, the incompensation may become so serious that the heart fails to meet its office, and the patient dies.

Angina Pectoris.—This is a very serious heart disease, which may not even be connected with a valvular defect. It consists of sudden attacks of intense pain, during which the heart may stop suddenly. It is probably often due to spasm of the arteries of the heart, which arrests the nourishment of the heart muscle. (The heart is not nourished by the blood in its chambers, but by a special set of blood-vessels, the *coronary vessels*, which are distributed in its walls).

Minor Heart Disturbances.—Besides these serious heart diseases, there are a number of nervous disturbances, which are often sufficiently alarming, but not serious.

Palpitation consists in the consciousness of the heart beat. It is often connected with attacks of indigestion.

Sudden but temporary cardiac weakness constitutes *syncope*—a form of fainting.

The abuse of tobacco is apt to bring on cardiac *irregularity*, which fortunately disappears when the drug is discontinued. Similar irregularities follow infectious diseases, for instance, influenza. During fevers, the heart is abnormally *rapid*, likewise in the dangerous exophthalmic goiter.

Diseases of the Blood-vessels.—The most common of these is *arteriosclerosis*—hardening of the arteries. This is a normal phenomenon of old age; but it may be brought on earlier by disease, syphilis and, perhaps, alcohol, tobacco, etc. It makes an extra resistance to the heart, and therefore interferes with the nourishment of the organs. It is often associated with kidney disease.

Aneurism is a dilatation of the artery where the arterial wall has been weakened. The weakened artery often ruptures. Aneurism of the aorta is therefore often fatal.

Paralysis of the vessels lowers blood-pressure; it may be to a dangerous degree, as in collapse and shock. It is generally due to a paralysis of the vasomotor center, but may involve other mechanisms.

CIRCULATORY STIMULANTS

Under this term are comprised remedies which improve the heart. These may have quite different mechanisms of action, some act directly on heart muscle, others act quite indirectly. This can be best appreciated by discussing them in groups.

Normal Saline Solutions.—These must not be confused with the "normal" solutions in volumetric analysis. They are solutions which are indifferent to animal tissues. The simplest is a 0.85 per cent. solution of NaCl (liquor sodii chloridi physiologicus, U.S.P.). More complex solutions are used for certain purposes; as Ringer's or Locke's. These contain some Ca, K, PO_4 and HCO_3, and sometimes glucose. As heart stimulants they are injected in the quantity ½ to 1 liter, under the skin, or directly into an arm vein. They act simply by supplying more fluid for the pumping action of the heart. This is useful especially when blood has been lost through hemorrhage. The same object may be accomplished,

but somewhat less effectually, by lowering the head and bandaging the legs and arms.

Digitalis Group.—This comprises digitalis and its principles; strophanthus and strophanthin; squill; apocynum; convallaria; adonis and some others of minor importance.

Actions.—These drugs constitute the so-called "cardiac tonics," since their action is to increase the contractibility or "tone" of the cardiac muscle, so that the heart executes more powerful strokes. At the same time the rate is slowed, especially in the overrapid heart, by vagus stimulation. There is also some tendency to vasoconstriction.

Uses.—These actions enable the heart to compensate more or less perfectly for any valvular defects; and the symptoms of heart disease are thereby relieved. The more effective blood flow also aids the secretion of urine, and thus causes the absorption of dropsies.

Toxic Effects.—The continued administration of these drugs leads to "*cumulative actions,*" since they are but slowly absorbed and their effects are quite lasting. In this way, toxic symptoms may arise, so that it is unsafe to give these drugs routinely, unless their effects can be carefully watched. The toxic symptoms begin with irregularities of the pulse or with nausea, headache, vomiting and diarrhea. When these appear, the administration must be interrupted. The treatment of acute poisoning would be by evacuation, brandy, and nitrites.

Digitalis Constituents.—Digitalis is the most important member of the group. It contains a number of glucosidal principles, of similar action. The most important is *digitoxin*, crystalline, but insoluble in water, causing strong local irritation and vasoconstriction, which are serious drawbacks to its use. *True digitalin* is also in-

soluble in water. *Digitalein* is soluble, and is probably the active ingredient of the proprietary digalen. The *commercial "digitalins"* are indefinite mixtures of these active principles. There is also a saponin, *digitonin*, which is important mainly since it renders digitoxin and digitalin soluble in water, so that they pass into the infusions.

Digitalis Preparations.—The *infusion* is considered the most suitable form by some physicians; but it is unstable.

The fluidextract does not completely represent the drug—another reason why it should not be used to make the other preparations. All things considered, the *tincture* is the most satisfactory. However, it deteriorates somewhat after a year.

Bio-assay of Digitalis.—Digitalis leaves vary considerably in strength, and the preparations are likely to vary still more. This is a very serious matter with drugs of such high potency. They should therefore be standardized. Since the activity is due to a number of active constituents, chemical assay is out of the question. Some form of bio-assay must be employed. Several fairly satisfactory methods have been proposed. The simplest is that of the U.S.P.IX. It consists in injecting a series of frogs with different doses, and noticing whether the dose is just sufficient to stop the heart in a particular way (systolic standstill) one hour after injection. The susceptibility of the frogs is controlled by testing them with ouabain, a crystalline strophanthin of uniform activity.

Other prominent methods of digitalis assay involve the determination of the doses that kill a standard weight of frog in twelve to twenty-four hours (Cushny-Houghton); the fatal dose for guinea pigs (Reed and Vanderkleed); the fatal intravenous dose for cats (Hatcher) is probably the most accurate method.

Strophanthus.—Its use by mouth has no advantage over digitalis, but rather otherwise, for its absorption is very uncertain. However, its active principle can be injected into a vein, and is therefore useful when a very prompt action is necessary. There are several different *strophanthins,* denoted by prefixing the first letter of the species from which they are obtained. The official is an amorphous glucoside from kombe strophanthus.

Strychnine.—Although classed as a cardiac stimulant, this does not act directly on the heart. Large doses produce a prompt stimulation of the vasomotor and respiratory centers and may in these ways benefit the heart indirectly. It is used in many forms of collapse, but it is very doubtful whether safe doses are effective. To secure rapid action, it is generally administered hypodermically.

Other Uses of Strychnine.—Strychnine stimulates the nerve centers of the spinal cord and medulla. It is used as a respiratory stimulant whenever respiration threatens to fail. It is employed in certain forms of muscular paralysis, but is harmful in others. Its tonic action on the spinal center is utilized by adding it to laxatives; in atony of various sphincters and muscles; in impotence. In these its value is probably small. It is useful as a general tonic, to improve the tone and nutrition of the muscles, and thereby the general health. Its stomachic effect aids in the tonic action.

Strychnine-poisoning.—This is characterized by very violent convulsions, due to excessive stimulation of the spinal centers. The spasms are brought on by some slight excitation—a light touch, jarring the floor, a sudden noise, etc. All the muscles of the body contract violently at the same time. The convulsions are therefore symmetrical; and since the back-muscles are the stronger, the body is arched backward—*opisthotonus*—

resting on head and heels. (Convulsions with body bent forward are *emprothotonus.*) When the convulsions are mild, the muscles contract and relax alternately, constituting "clonic spasms;" when the spasms become more severe, the muscles remain contracted—"tetanic." Strychnine convulsions are very similar to those of traumatic tetanus—a tetanus produced by the toxin of the tetanus bacillus. The main difference is that traumatic tetanus develops more slowly and is more persistent, and is more often confined to one set of muscles, as in "lockjaw."

Treatment of Strychnine-poisoning.—Any remaining strychnine should be oxidized by permanganate. If the patient is seen before the convulsions, the stomach should be washed. When convulsions have started or are threatened, artificial respiration should be instituted and kept up even between convulsions. Chloroform or ether should be inhaled to lessen pain and save the strength of the patient. Chloral accomplishes a similar purpose.

Other Convulsants.—Convulsions are produced by many poisons and diseases which stimulate the central nervous system. The stimulation may be either in the brain, the medulla, or spinal cord. These differ considerably in type.

Spinal convulsions are typified by strychnine, *i.e.*, by symptoms of tetanus, with opisthotonus. They are also produced by traumatic tetanus, caffeine, hydrastine and morphine.

Medullary convulsions are typified by asphyxia. They are irregular and asymmetrical. They are produced by asphyxial gases: cyanide; camphor; cocaine; picrotoxin ; veratrine, etc. Similar convulsions are sometimes seen in uremic poisoning and in eclampsia.

Cerebral convulsions are typified by epilepsy. They

generally begin with twitching of single groups of muscles. The symptoms are closely related to the medullary type; some of the drugs enumerated under medullary convulsions would also be counted here. Often the same drug acts on all the centers.

Caffeine.—This alkaloid, which is important as a constituent of coffee and tea, stimulates the respiration much like strychnine, and is safer. It also stimulates the circulation, mainly by a direct action on the heart. It increases the urine flow, as will be discussed later. It is therefore useful in dropsies. It stimulates ordinary muscle, and counteracts fatigue. Unlike strychnine, it stimulates also the higher centers of the brain, and produces excitement, wakefulness, etc.

Picrotoxin.—This is a neutral principle, occurring in Cocculus indicus ("fish-berries"). It stimulates the convulsive centers of the medulla, as also the other medullary centers, those of the respiration, blood-vessels, etc. It is quite toxic and has been used as "knock-out drops." It is sometimes employed internally against night-sweats, and externally against pediculi; but it is not quite safe.

Other convulsants will be discussed in other connections.

Atropine.—This alkaloid and the drugs containing it (belladonna, hyoscyamus, etc.) act as circulatory stimulants mainly by quickening the heart-beat. The effect is produced by paralysis of the vagus nerves in the heart. The more rapid strokes of the heart throw out more blood, especially when the previous rate was abnormally slow. In this way the whole circulation is quickened.

Atropine has a number of other important actions. Some of these have been discussed, viz., the regulation of cathartics, the stimulation of the respiratory center

and the control of asthma. Other actions, especially that on the eye, will be mentioned later.

Camphor.—This is given hypodermically (1 c.c. of the sterile oil or spirit) as a cardiac stimulant and in collapse. Its action is rather uncertain, but it sometimes seems to be of value.

It will be recalled that it is also used largely as a mild counterirritant, as discussed under rubefacients.

Ammonia.—This is one of the best examples of the *diffusible stimulants* or *analeptics*. It acts very promptly, mainly by reflex stimulation of the respiratory and vasomotor centers in the medulla oblongata. This results in a prompt and considerable, but brief, improvement of the circulation and respiration, which is useful in fainting, acute cardiac collapse, etc. It may be employed in the form of ammonium carbonate (smelling salts) or aromatic spirit of ammonia, by inhalation, or by mouth (diluted).

Reflex Medullary Stimulants.—Other volatile counterirritants may also be used for the same purpose as ammonia: volatile oils (aromatics, vinegar, etc.); ether (Hoffmann's anodyne); compound spirits of lavender; etc. The burning of feathers is a popular method of medullary stimulation in fainting.

Ammonium Salts.—These may stimulate the medullary centers directly, but this action occurs only when they are injected into a vein, not when they are administered by mouth. They are therefore of no practical use for this purpose, although they have other uses: ammonium acetate as diaphoretic (liq. ammonii acetatis, "spiritus mindereri"); ammonium carbonate and chloride as expectorants.

Alcohol.—This acts sometimes as a circulatory stimulant. The effect is mainly due to reflexes from its local irritant actions; but the food value of alcohol may also

help the heart. Further, it dilates the vessels and this lessens the work which the heart must do.

Ether.—This acts mainly as a prompt reflex stimulant. It may be used hypodermically in emergencies; but more commonly it is taken by mouth, in the form of the spirit or compound spirit, or "Hoffmann's drops." (The latter contains the so-called "oil of wine"—an indefinite mixture which was laudably omitted from the current Pharmacopeia.

Ergot.—This is sometimes given to constrict the blood-vessels; but is of doubtful value for this purpose. It has already been mentioned.

Epinephrin.—The *suprarenal glands* are situated near the kidneys. They contain an active principle, related to the alkaloids, and marketed under the trade names of adrenalin, etc. It has no effect when given by mouth, and is almost ineffective even when injected hypodermically. When it is injected into the muscles or especially into the veins, it produces a very high rise in blood-pressure, mainly by contracting the vessels, but the heart is also somewhat stimulated. It may therefore be injected into the veins to stimulate the circulation in acute collapse conditions. However, its use in this way is rather dangerous, since an overdose easily overtaxes the heart.

It is used hypodermically against asthma; and locally against superficial hemorrhage, and sometimes to constrict the blood-vessels in catarrh, hay-fever, etc. Its actions, however, are very short, and it should always be used under supervision. It is also used to intensify and prolong the action of local anesthetics.

Suprarenal preparations may be standardized according to the U.S.P. IX, by injection into the veins of an animal. The rise of blood-pressure is compared with that produced by the injection of a known dose of a standard preparation.

Pituitary.—Extracts of the posterior lobe of this gland are inactive by mouth; but when injected intramuscularly or into a vein, they stimulate the blood-vessels, uterus, intestines, bladder, etc. Their usefulness in shock and collapse is doubtful, since they depress the heart.

CIRCULATORY DEPRESSANTS

Manner of Action.—The circulation can be depressed by weakening or slowing the heart; or by dilating the blood-vessels.

A direct weakening of the heart muscle is produced by a number of poisons; but the doses required are too dangerous. Such cardiac depressants have therefore a very limited field. The most important is potassium.

Potassium.—Potassium salts depress the heart and the central nervous system when they are injected intravenously. By mouth, however, therapeutic doses have no systemic effect, because the capacity for excretion is greater than the absorption. They therefore act only like the corresponding sodium salts. With poisonous doses, however, the absorption may be sufficiently great to produce the real potassium action.

Slowing of the Heart.—This is a much more feasible way of depressing the circulation. It may be accomplished without danger by drugs which stimulate the vagus, the restraining nerve of the heart. The most important are aconite and veratrum. This slowing of the heart may be useful when the heart is overexcited in fever; when the heart is inflamed, etc. The depression of the heart tends to lower temperature.

Aconite.—Small doses slow the heart and are used to lower the temperature in the early stages of acute fevers, especially colds. The benefits are perhaps rather doubtful. It is not used in the later stages, because the depression may easily pass into collapse.

Aconite also has a local irritant action, producing a sensory stimulation, with prickling sensation, etc. This explains its local use in neuralgias, rheumatism, toothache, etc.

The principal active constituent of aconite is the alkaloid *Aconitine.* This tends to decompose into less active alkaloids. Commercial "aconitines" often consist of such mixtures, of uncertain activity, and are therefore dangerous. This is one reason why aconitine is so rarely used.

Bio-assay of Aconite.—The galenic preparations also vary greatly in activity. The alkaloidal assay is of little value, since the alkaloids often consist of the inactive degeneration products. The determination of the minimal fatal dose for guinea pigs, as advised in the U.S.P. IX, gives fairly satisfactory data. The prickling taste is a useful rough test of activity (Squibb's test; Ford, Ford and Wine, Am. Jour. Pharmacy, 87 : 489).

Toxicology of Aconite.—Aconite is a highly fatal poison. Overdoses produce tingling of the tongue and skin; vomiting and diarrhea; extreme irregularity of the pulse; great anxiety; collapse and death. The treatment consists in evacuation and stimulants, keeping the patient warm.

Veratrum and Veratrine.—The alkaloid veratrine is not derived from veratrum, as the name would suggest. It is a mixture of alkaloids derived from related plants. Its actions are similar to veratrum, and resemble those of aconite. Veratrum is used internally to slow the pulse and to lower the blood-pressure. Veratrine is too irritant for internal use, but is sometimes employed externally as an ointment, for counterirritation in neuralgia, etc.

The toxicology of veratrum and veratrine is similar to that of aconite.

We may take this occasion to dispose of a number of drugs which are more or less similar, although they would scarcely be classed as cardiac depressants.

Conium.—The hemlock plant (not the hemlock tree) contains coniine and a number of other related alkaloids. It produces collapse and paralysis. It was formerly used as an antispasmodic, but is now obsolete. It is supposed to have been the poison that was administered to Socrates.

Gelsemium.—Jasmine root contains a number of alkaloids of diverse action. The tincture is sometimes given internally against neuralgia. One alkaloid dilates the pupils on local application. It is, however, too irritant.

Tobacco and Nicotine.—The effects of tobacco, however it may be used, are due to the alkaloid nicotine. This stimulates and paralyzes various parts of the nervous system, central and peripheral, and thus produces a great variety of symptoms.

Acute Poisoning.—The immediate effects consist in nausea, vomiting, and diarrhea, and great prostration. With larger doses, there are also disturbances of respiration and circulation; profound collapse; convulsions; and often a rapidly fatal ending. Death from its medicinal use by the laity has not been uncommon.

Nicotine Habits.—By its habitual use a considerable degree of tolerance is acquired against the acute gastrointestinal effects. In the habituated users of tobacco, nicotine within the limits of this tolerance produces little immediate action, beyond the feeling of comfort and satisfaction in its use.

The question whether the use of tobacco within these limits is harmful, cannot be easily answered. There is evidence of its harm in young people, especially in children, who are more susceptible to its actions; but with many older individuals, who have used tobacco in

moderation, it would be very difficult to point out any serious detrimental results that could be attributed to the nicotine with any degree of certainty. However, there is often some irritation of the respiratory passages; some digestive disturbances and impairment of nutrition, and some nervous irritability.

The principal objection to tobacco is that its use is apt to exceed the limits of moderation. In that case, these deleterious effects become much more pronounced, and other manifestations set in. Perhaps the most common is irregularity of the heart—"tobacco heart." More serious is the occasional occurrence of blindness in inveterate excessive smokers. The irritation of the smoke, particularly from pipes, predisposes to cancer of the tongue.

With the exception of the last, these nicotine effects disappear completely if the habit is discontinued or at least restricted, before they have gone too far. This is their proper treatment.

Lobelia.—This acts rather similarly to nicotine. It was used as a nauseant and emetic. It is inferior to other drugs, being disagreeable and rather dangerous.

Colchicum.—This is used mainly in the treatment of acute attacks of gout. Opinions vary as to its usefulness. Toxic doses produce violent bloody diarrhea, which is difficult to treat, and often fatal.

Vasodilation.—The blood-pressure is kept up by the heart pumping against the blood-vessels. When these are narrowed, the resistance is increased and the blood-pressure rises. When the vessels are dilated, the blood-pressure is lowered. Certain diseases are characterized by excessive constriction of the vessels, notably arterio-sclerosis and certain forms of Bright's disease. A spasmodic constriction occurs in certain headaches and in angina pectoris. Some poisons also produce constriction,

especially lead and barium. Furthermore, even a normal tone of the vessels may be too much for weak hearts. In all such cases it becomes desirable to dilate the blood-vessels. This may be done by the nitrites, or by organic nitrates, such as nitroglycerine, which are reduced to nitrites in the body.

Nitrites and Organic Nitrates.—These dilate first the skin vessels, resulting in blushing. Then the vessels in the skull, producing headache; then the abdominal vessels, causing a fall in blood-pressure. The heart is quickened. Overdosage produces collapse and methemoglobin formation, hence cyanosis. The main differences between the members concern the rapidity of their action:

Amyl nitrite, which is usually administered by the inhalation of a few drops on a handkerchief, lowers the blood-pressure in a few minutes. The action lasts only five or ten minutes. It is employed especially in angina.

Nitroglycerine (*Spir. glycerylis nitratis*) *and sodium nitrite* act in ten or fifteen minutes and last perhaps one-half hour. They must, therefore, be given at frequent intervals. Nitroglycerine is the form used especially in arteriosclerosis. It gives relief unless the arteries are extensively calcified; but its efficiency generally wears off after a time. It is therefore usually supplemented by potassium iodide.

Sodium nitrite is somewhat irritant because of the liberation of nitrous acid in the stomach. It is said to cause less headache.

Erythrol tetranitrate is much more lasting in effect, persisting several hours. It produces more headache than others.

Ethyl nitrite in the form of sweet spirit of niter also belongs to the group; the ordinary doses are too small to lower blood-pressure. It is employed to dilate the skin

vessels, thus helping diaphoresis, for example, in light fevers.

Nitrites are also used in asthma, and sometimes in internal hemorrhage, but in the last condition they may do more harm than good.

DIURETICS

Importance of Urine Secretion.—The urine has the function of removing useless and poisonous waste products from the body. It is a watery solution, containing urea, uric acid and other nitrogenous substances (in part unknown); other organic substances; and inorganic salts. The latter are derived partly directly from the food; partly from the metabolism of the tissues.

All these substances would become toxic if retained in the body in excessive amount—some more so than others. Suppression of the urine secretion is therefore fatal in a few days with the symptoms which are grouped together under the name of "*uremia.*" The most serious of these are convulsions and coma. They occur in Bright's disease (inflammation of the kidneys or nephritis). An important variety of this disturbance called *eclampsia,* occurs sometimes in pregnancy. Another important phenomenon of kidney disease is the formation of *dropsies,* also called *edema* or *hydrops.* If liquid accumulates under the skin, it is called *anasarca;* if it is confined to the serous cavities, (for instance, the peritoneum), it is called *ascites.* Dropsies may be due either to kidney or heart disease.

Action of Diuretics.—Diuretics increase the flow of urine, and thus remove fluid and waste products from the body. They are much more effective when the kidneys are involved only secondarily, as in heart disease, than when there is real kidney disease. To understand this

and their whole mechanism of action, we must review briefly the mechanism of urine formation.

Structure of the Kidneys.—The blood-vessels here have a peculiar arrangement. The small arteries first break up into a twisted ball of the capillaries, the *glomeruli*. These are surrounded by a little bag (Bowman's capsule) formed by very thin endothelium. The blood is filtered through this thin endothelium into the interior of the bag. The filtrate differs in some important respects from the blood; the corpuscles and proteins have been removed, and the proportion of the other constituents has perhaps been changed, although our information as regards this is not definite.

The endothelial bag is prolonged into a long and very twisted tubule, along which the first urine passes, and where it undergoes further modifications. These tubules are lined with a higher epithelium, which modify the filtrate by the absorption of certain constituents, and possibly by the excretion of others.

The capillaries of the glomeruli unite into arteries, which then break up into a second set of capillaries, surrounding the tubules. The tubules unite into larger ducts and finally empty into the cavity of the "pelvis" of the kidney. From here the urine flows along the ureters into the bladder, where it remains until voided.

The Formation of Urine.—For simplicity this may be considered a peculiar filtration process. As in all filtrations, the rapidity and the quantity of the process is determined mainly by two factors: (1) The character of the filtering membrane—in this case cells of the kidney; and (2) the filtration pressure, *i.e.*, the blood-pressure. The blood-pressure is affected by anything which alters the circulation, as also by local diseases of the kidney. The cells may also be rendered more permeable by certain drugs, and less permeable by others. They are less

permeable in most nephrites (inflammation of the kidneys), and may even become impermeable. In that case, the filter ceases to work, the urine is suppressed and cannot be started until the cells recover their permeability. Diuretics would, therefore, be useless; it is only possible to relieve the kidneys of their work by stimulating the sweat by diaphoretics and the intestines by cathartics.

Diuretics or drugs which increase urine flow may act by modifying either the circulation or the kidney cells—sometimes both. They will be discussed seriatim.

Digitalis and Related Drugs.—These are diuretic solely when they improve a defective circulation. They are therefore efficient only in heart disease. Here they surpass greatly the other diuretics, and lead to a large output of urine, the absorption of dropsies, etc. *Digitalis* and *strophanthus* are the principal representatives. *Squill*, which belongs to the same class, possibly irritates the kidneys somewhat. *Apocynum* is nauseant.

Caffeine, Theobromine and Theophylline.—These are methyl derivatives of a substance called xanthin; caffeine being trimethylxanthin. The others are dimethylxanthin. They are rather better known by their trade names: theobromine-sodium salicylate as diuretin; theophylline-sodium acetate as theocin.

These methylxanthins all increase the urine flow by a direct action on the kidneys. Their diuretic effects are variously attributed to direct stimulation of the kidney cells, or to dilation of the kidney vessels. Their action is fairly powerful but rather uncertain. The theophylline is the most, caffeine the least effective. They are largely employed as adjuvants to other diuretic measures, to help the elimination of fluid in dropsy, especially in cardiac disease. Their efficiency in heart disease depends partly on a direct stimulant action of the cardiac

muscle. They increase the force of the cardiac contractions, at the same time dilating the blood-vessels and so lowering the resistance to the heart. Ordinary muscle is also rendered more efficient and less easily fatigued. Muscular work is therefore facilitated.

There is also central stimulation expressed by wakefulness, excitement, etc., and in large doses by convulsions. These central actions are much more prominent with caffeine than with the others, and limit its usefulness as a diuretic. However, this stimulant action is useful in acute alcohol or morphine-poisoning.

Caffeine Beverages.—Caffeine is the principal active constituent of various popular beverages: coffee, tea, cola, guarana, etc. Theobromine occurs in cocoa and chocolate. The stimulant action of the beverages is largely due to the caffeine although it is somewhat modified by the other constituents: in tea by the astringent effects of the tannin and the excitant action of the volatile oil; in coffee by the irritant and stimulant action of the aromatic empyreumatic products of roasting. These modify the effects somewhat, especially on the digestive organs; tea being constipating, coffee rather laxative.

However, the deleterious effects of excessive tea or coffee consumption are mainly due to the caffeine. They consist in wakefulness, palpitation, headache, and indigestion.

Irritant Diuretics.—These irritate the kidneys and are therefore usually inadvisable in kidney diseases proper. They are employed more often to flush the urinary passages and bladder with urine, for instance, in vesical catarrh. They are usually also antiseptic.

Examples of this class are *juniper*, *cubeb*, *copaiba*, *santal*, *buchu* and *uva ursi*. The latter contains a glucoside, arbutin, which is decomposed in the urine with the

liberation of the antiseptic hydroquinon. *Alcohol* and *formic acid* may also be counted as irritant diuretics.

Calomel, in rather large doses, is often an efficient diuretic in cardiac and hepatic dropsies.

Scoparius—broom tops—contains a diuretic glucoside, scoparin. It also contains the alkaloid *spartein.* This is used in cardiac diseases. It slows and weakens the heart, and is therefore not a real digitalis substitute.

Water.—This is mainly eliminated by the kidneys, and therefore increases urine flow, unless the renal filter has become impervious by disease. *Milk* is a still more effective diuretic because of the milk sugar.

Diuresis by increased income of fluid would, of course, be useless in dropsies; but it is valuable particularly for the removal of toxic substances in uremia, and for preventing the formation of calculi or stones in the kidneys or bladder.

Saline Diuretics.—The salts of alkalies are generally excreted by the kidneys, and carry a certain amount of water with them. They are therefore diuretic by osmotic action. In addition they probably have a direct stimulant or irritant effect on the kidneys. While all absorbable salts produce this effect, *potassium nitrate and iodide* are particularly employed.

The Salts of Organic Acids.—*Acetates, citrates, etc.,* are oxidized in the tissues into carbonates, and therefore act as alkalies. These also have a considerable diuretic action, and make the urine alkaline, and therefore less irritating. This is utilized, for instance, in catarrh of the bladder. It also prevents the deposition of uric acid, gravel, or calculi in the urine. Other alkalies, the bicarbonates, carbonates and even hydroxides, have been used for this purpose, but their alkaline action on the stomach is often undesirable.

Organic alkalies—*diethyldiamin* or *piperazin*—are also

prescribed as "urate solvents," but have not been of material advantage.

Urate Solvents.—Uric acid forms relatively insoluble salts, which tend to precipitate in the tissues (as the chalky nodules or "tophi" of gout), and in the urine as gravel or stones. Some years ago, there was a tendency to attribute a large group of common ailments to a "uric acid diathesis," *i.e.*, to an abnormal tendency to retain and precipitate uric acid. It was therefore aimed to find remedies which would increase the elimination or solubility of the urates. This led to the introduction of numerous uric acid solvents and eliminators.

Further experience showed, however, that these theories were untenable. The only disease in which uric acid in the tissues has been shown to play a part is gout; and here it is probably as a mere side effect and not a cause. On the other hand, the remedies which were supposed to dissolve the uric acid were found to be ineffective in the tissues. In the test-tube, it is quite easy to dissolve uric acid, for instance, by means of lithium carbonate; but this cannot occur in the presence of sodium salts, such as exist in all the tissues. In the urine, alkalies are effective in preventing the precipitation of uric acid, but not in dissolving it when once precipitated.

Several agents have been found which increase the *elimination of urates. Salicylates* have this action and particularly the new drug *phenylcinchoninic acid* (Atophan). The latter has been found effective in gout and rheumatism, but its efficiency is probably due to an analgesic action and not to the removal of uric acid. It sometimes produces skin eruptions.

Kidney and Bladder "Stones."—These "calculi" are formed by the precipitation of the urinary constituents, particularly the urates and oxalates (in acid urines), or phosphates (in alkaline urines). After the solid stones

or calculi are once formed, it is probably impossible to dissolve them, and they must be removed by surgery. It is possible, however, to diminish the tendency to their formation, or the increase in size by dilution of the urine, through the administration of water, and by controlling the reaction of the urine; keeping it alkaline if there is urate or oxalate precipitation and acid in case of phosphate deposition. Control of the diet is also important.

Renal Colic.—When a renal calculus becomes lodged in the ureter, it gives rise to attacks of excruciating colicky pain. This is treated by the application of heat; morphine to lessen the pain, and atropine to relax the ureter and hasten the passage of the stone. The same treatment applies to *biliary colic, i.e.*, the passage of gallstones.

"Kidney Cures."—Many remedies are sold for so-called kidney diseases. These do vastly more harm than good. Real diseases of the kidneys are very serious conditions, in the treatment of which drugs play only a minor part—attempts to treat them by drugs alone invariably hasten the death of the patient. As a matter of fact, however, the conditions for which these mixtures are taken are not usually kidney disease, but bladder trouble, or wholly imaginary complaints. Here the damage is perhaps less direct, but it is very undesirable to create imaginary kidney diseases.

DIAPHORETICS; ANHYDROTICS; SIALAGOGUES: STERNUTATORIES, ANTIPYRETICS

Diaphoretics.—These are remedies which promote sweating. Sweat is a secretion of the sweat-glands, numerous small glands located under the skin and distributed over the body. Their secretion may be promoted either by increasing their blood supply; or by stimulating the nerves with which they are supplied.

The most important diaphoretic measures are the following:

Heat.—This is the usual physiologic stimulus for the sweat-glands, and may be used therapeutically to increase their activity. It is applied externally, as hot baths, hot packs, etc.; or internally as hot drinks. The drinks are rendered more effective and less disagreeable when containing alcohol or aromatic substances, as the various "teas" used in domestic medicines. Hot drinks are also diuretic.

Nauseants.—Sweating is a prominent effect of nausea. This action is utilized in the *Dover's powder.* In this. however, the opium also plays a part, since morphine dilates the skin vessels and therefore the blood supply of the sweat-glands. The action is relatively mild. This is true also of ammonium acetate, spirits of nitrous ether, and alcohol. These mild effects are used mainly in slight fevers, the dilation of the skin vessels and the evaporation of the sweat producing a moderate *antipyretic effect.* Conversely, the coal-tar antipyretics and the salicylates produce diaphoresis.

Pilocarpine.—This is a very powerful diaphoretic, stimulating the nerves of the sweat-glands directly. It also stimulates other "sympathetic" nerves, and therefore produces salivation and increased flow of mucus; contractions of the stomach and intestines (vomiting and diarrhea); contraction of the pupils; slowing and quickening of the pulse, etc. It is antagonistic to atropine. In susceptible individuals it may cause fatal edema of the lungs and should therefore not be used indiscriminately. It is best administered hypodermically.

Uses of Diaphoretics.—Sweating is employed against colds and fevers; to relieve the kidneys; to remove fluid from the body in dropsies; and to promote the elimination of certain poisons, for instance, lead and mercury.

Anhydrotics.—These cause suppression of perspiration. Locally (for instance, in case of sweating of feet, etc.) this can be accomplished by astringents, often with the addition of antiseptics. Agents of this kind are alum, dilute acids, alcohol and boric acid. Salicylic acid is not advisable, since it corrodes the skin. Talcum is useful as an absorbent of the secretions.

Excessive sweating of the whole body may occur in fevers. The drenching *night-sweats* of consumption are especially exhausting. They may also be treated by sponging with vinegar, alcohol or tannin, or more effectively by *atropine.* This paralyzes the nerves of the sweat-glands, and produces other side-actions which greatly limit its application. *Agaricin* acts similarly, but is inconstant. *Camphoric acid,* which is sometimes used, is probably ineffective.

Sialogogues.—These increase the flow of saliva. A reflex salivation is produced by the taste of acids, ether and other irritants, as by the nauseants. The salivary nerves can also be stimulated directly by pilocarpine. However, there are few if any therapeutic indications for sialogogue action.

Excessive salivation ("*ptyalism*") is a distinctive feature of chronic mercury-poisoning.

Sternutatories.—These produce sneezing. Ordinary snuff, pepper and veratrine are examples. They are obsolete in therapeutics.

Antipyretics.—These are drugs which lower the temperature in fever. The body temperature of warm-blooded animals is very constant, being maintained by a delicate adjustment of heat production to heat dissipation, somewhat as the temperature of a thermostat may be regulated either by adjusting the burners or by opening or closing the door. Heat is produced by the chemical changes of the tissues as a by-product of the work of

the body. Heat is dissipated from the lungs and skin, particularly by the evaporation of the sweat. The heat loss is controlled by the amount of blood in the skin, which exposes more or less blood to the cooling effect of the air and by the amount of perspiration.

In fever, the heat regulation is disturbed, so that there is both an increased combustion and a diminished loss. This disturbance may then be regulated either by diminishing the production of heat or by increasing the loss of heat. Some antipyretics act in one way and some in the other. They have but little effect on normal temperature since the normal heat regulation counteracts their effects.

The principal antipyretic drugs have already been discussed, namely, acetanilid, acetphenetidine, antipyrine, salicylates and quinine. Aconite and veratrum are also used; these act, less effectively, by slowing the heart, thus lessening the heat production.

DRUGS WHICH ACT ON THE PUPILS

The diameter of the pupil is controlled by the contraction of the muscles of the iris. There are two sets of muscles, circular and radial. The pupil can be narrowed by contraction of the circular muscles, which are innervated by the oculomotor nerve; they can also be narrowed by the relaxing of the radial muscles, which are innervated by a sympathetic nerve. Dilation of the pupils would occur by relaxing the circular or stimulating the radial muscles.

The oculomotor nerve also controls the muscles which adjust the diameter of the lense by which the eye is accommodated to near or far objects. Stimulation of the oculomotor, which constricts the pupils, therefore also makes the eye near-sighted; and paralysis of this

nerve makes it far-sighted. Drugs which dilate the pupil, such as atropine, are called *mydriatics;* those which constrict the pupils, such as physostigmine, are called *miotics.* These drugs are important in eye-practice, and as symptoms of poisoning.

The principal drugs which act on the eye are the following:

Mydriatics (dilation of pupils) *by paralysis of oculomotor nerve:*

Atropine
Hyoscyamine
Scopolamine
Homatropine
Euphthalmine
Eumydrine
Gelsemium

Mydriatics by stimulation of sympathetic nerve:

Cocaine
Epinephrine
Asphyxiants

Miotics (constriction of pupil) *by stimulation of oculomotor nerve:*

Physostigmine
Pilocarpine

Miosis by central action:

Morphine

Edema of eye (used against certain eye diseases):

Ethylmorphine (Dionine)

Eye Waters (Collyria).—These should be freshly made, and filtered, to exclude any irritant dust, etc. Those used against conjunctivitis (inflammation of the surface

of the eye) usually contain boric acid or zinc sulphate, sometimes silver nitrate and cocaine.

ANESTHETICS

The central nervous system may be compared to a telephone exchange with constant incoming and outgoing messages in the form of nerve impulses. The outgoing or efferent impulses go to the muscles, glands, etc., and produce motion, secretion, etc. The incoming or afferent impulses are the sensations of sight, sound, temperature, etc., that is, the special senses. One of these special senses is that of pain.

Agents which abolish all sensation (including pain, touch, etc.) are called anesthetics; those which abolish pain, without materially affecting the other sensations, are called anodynes or analgesics. Just as the telephone message may be interrupted at the sending or receiving station, so the nerve impulse may be interrupted at the periphery or in the central nervous system.

We therefore have local and general anesthetics.

LOCAL ANESTHETICS AND ANODYNES

Agents which paralyze sensation at the periphery, by local contact, are called local anesthetics. The most important of these is:

Cocaine.—This is capable of paralyzing any nerve which it touches. Weak solutions, however, have a special affinity for sensory nerves; so that, under proper conditions, it acts upon sensation exclusively.

To produce this anesthetic action, it must, of course, come into actual contact with the nerves. It is readily absorbed from mucous membranes, and therefore produces local anesthesia of these on simple application.

It is not absorbed from intact skin, and here it would be ineffective. Given by mouth, it would be too greatly diluted before reaching the nerves, so that the action would be slow and ineffective.

For most operations it must therefore be injected hypodermically into the field of operation. However, when it is injected into the spinal canal, it paralyzes all the nerve roots, and hence produces a general anesthesia without loss of consciousness. This *spinal anesthesia* has a field, particularly where the ordinary general anesthetics are contraindicated, but it is not without danger.

Cocaine is readily absorbed from mucous membranes and subcutaneous tissue; and in proportion as it is absorbed, the local anesthetic effects disappear and systemic toxic effects tend to develop. It is therefore desirable to lessen its absorption. This may be done by slowing the local circulation, on which absorption mainly depends. In operating on a finger, for instance, this may be done by a tight ligature. Where ligatures cannot be applied, the same object is secured by constricting the blood-vessels by the addition of epinephrin. Cocaine itself produces some vasoconstriction, and incidentally also dilates the pupil.

In any case, the action of cocaine is short, and the anesthesia is therefore only adapted to operations, not for continued pain. A further limitation to its continued use is set by the tendency to create the dangerous habit. This should prohibit the employment in catarrh and hay-fever remedies. The prompt relief which it gives is purchased at the cost of ultimate misery. On the other hand, it is a useful ingredient in eye washes against acute conjunctivitis, foreign bodies, etc.

Extracts of cocoa leaves have been used as a stimulant, but since they seem to owe their action to the cocaine they are too dangerous to be permitted. The effects

of cocaine-free coca extracts are not scientifically known.

Toxicology of Cocaine.—Acute and chronic poisoning are both important.

Acute cocaine-poisoning is not infrequent in the therapeutic use, when the drug is injected or strong solutions applied to the mucous membranes. Some persons are over-susceptible. The symptoms are: fast pulse, nausea and vomiting; headache, pallor and collapse; convulsions, dilated pupils. The treatment is by stimulants.

Chronic Cocaine-poisoning, or Cocaine Habit.—This is unfortunately quite prevalent. Each dose produces a general stimulation and excitement, often to delirium and hallucinations. The continued use leads to insomnia, moral degeneration, digestive disturbances, emaciation, lowered resistance, and an uncontrollable craving. Sudden withdrawal produces violent reaction and sometimes collapse. The symptoms are apt to be more serious even than those of morphine and therefore more difficult to treat. The treatment must be institutional, and along the same lines which will be discussed under morphine.

Cocaine Substitutes.—A considerable number of organic substitutes have actions similar to those of cocaine. *Eucaine, tropococaine, novocaine, stovaine,* and *alypine* may be named. They are slightly superior to cocaine in that they are rather less liable to produce acute poisoning, and are more easily sterilized, but the difference in toxicity is not great. As to sterilization, it was formerly believed that cocaine is destroyed by boiling its solutions, but it has now been shown that the destruction on short boiling is so slight as to be negligible.

Quinine urea hydrochloride produces a much more lasting anesthesia. Solutions stronger than 1 per cent. may produce sloughing.

Orthoform occupies a somewhat different field. It is very slightly soluble, so that its acute effects are small. Its action is continuous. It is therefore used, with rather limited success, as an anesthetic dusting powder for painful wounds, ulcers, etc.

Ethyl chloride spray is used to produce local anesthesia by freezing.

Other Local Anesthetics.—A number of other drugs have local anesthetic actions. They are generally much less efficient than cocaine. On the other hand, they do not share its dangers, so that they can be employed when a more continued action is desired; for instance, against itching, neuralgia, rheumatism, etc.

Hydrocyanic acid, although effectively anesthetic, is too toxic to be available. Its toxicology has been discussed previously.

Belladonna Group.—The solanaceous alkaloids produce a much weaker but much more lasting anesthesia than the cocaine. Belladonna, as fluidextract, liniment and plaster, is used especially against neuralgia, rheumatic pains and hemorrhoids.

Aconite.—This produces a brief irritation (tingling), followed by rather lasting anesthesia. It is used against toothache and neuralgia, as liniment or ointment. Its toxicology has been discussed.

Veratrine acts similarly. It is rarely used, because it has a high toxicity. *Colchicum* is used in acute gout.

Phenol.—Aside from its antiseptic and stimulant actions, this causes a brief tingling, followed by anesthesia. This adds to its value as an application for wounds. Its toxicology has been discussed.

Counterirritation.—Distraction of attention is one of the most efficient means of mitigating pain. Examples are the use of counterirritant aromatic oils in toothache, colic, neuralgia, etc.

GENERAL ANESTHETICS

Certain substances have the property of depressing the brain so as to produce unconsciousness, and thereby complete anesthesia. These are widely used for surgical operations. The margin between unconsciousness and death is not very wide; this makes it desirable to control the dosage quickly. This is a distinct advantage for the anesthetics which can be administered by inhalation; for the lungs absorb and excrete more rapidly than any other channel. Ether, nitrous oxide and chloroform have therefore kept in the lead, although non-volatile anesthetics are somewhat used, such as morphine with or without scopolamine, chloral, etc.

Inhalation Anesthetics.—Nearly all volatile aliphatic compounds are available for anesthesia; but practically the choice has become confined to relatively few, namely:

Ether.—This is the easiest to administer, and is also the safest, except nitrous oxide.

Chloroform.—This is quicker and more pleasant, but also much more dangerous.

Nitrous Oxide Gas.—This is probably the safest anesthetic. It is easily used for short operations; but its prolonged administration requires special experience and expensive apparatus.

Ethyl chloride, methyl chloride, etc. also act very rapidly, but are rather dangerous.

Mixtures of anesthetics—such as the alcohol-chloroform, ether (A.C.E.) mixture cause rather uncertain effects, since their constituents do not evaporate with equal rapidity.

Administration of Anesthetics.—Volatile anesthetics are administered by inhalation, being dropped on some sort of inhaler; usually a cloth held over the mouth,

and nose by a suitable frame or mask. The amount inhaled can be adjusted either by the rate of dropping or by the distance of the mask from the face.

Stages of Anesthesia.—The patient passes through a series of stages, which are essentially alike for all the anesthetics, except with regard to the quickness with which they are induced. Chloroform acts much more quickly than ether.

First there is more or less excitement and struggling; then confusion and incoherence. Then comes the anesthetic stage proper; and finally, if the anesthetic is pushed too far, the paralytic stage which terminates in death.

Anesthetic Stage.—In this the patient is entirely unconscious and relaxed, but the vital functions go on practically unimpaired. The respiration is slow but regular; the heart is strong; the blood-pressure normal with ether, but falls gradually with chloroform.

Fatalities.—These are much more common with chloroform than with ether; the effective and fatal dose lie closer together. Death may occur in two different ways: (1) Before anesthesia is established, by stoppage of the heart; this is the most common type of chloroform death. (2) In the paralytic stage, generally through paralysis of respiration, sometimes by stoppage of the heart, especially when this is diseased.

Fatalities are sometimes due to inexperienced administration; to too concentrated vapor; to unequal anesthesia, etc.; sometimes to special susceptibility; and sometimes perhaps to impurity of the anesthetic.

The *treatment of accidents* consists mainly in artificial respiration and reflex stimulation. Often atropine and morphine are given for prevention. Atropine prevents reflex stoppage of the heart; and with morphine less anesthetic is needed and the anesthesia goes more smoothly.

Accidents have also been occasioned by the inflammability of ether vapor. Chloroform is not inflammable, but in the presence of open light, but it gives rise to toxic oxidation products.

After-effects may cause serious damage. Both ether and chloroform irritate the respiratory and urinary organs, and may produce bronchitis or nephritis, especially if the lungs or kidneys are already diseased. Otherwise, there is not much danger if they are carefully given. The most serious effects occur if chloroform anesthesia is long continued. This may lead to fatal degeneration of the liver.

Choice of Anesthetic.—Ether is far safer than chloroform, and is therefore more often administered in this country. Chloroform is more pleasant and more prompt; so that it has some special uses. If given by an experienced anesthetist, its use is reasonably safe.

Contraindications.—Both anesthetics are dangerous in kidney, lung and heart disease. These leave a field for other anesthetics, which is fairly filled with spinal anesthesia with cocaine or similar substances. Large doses of morphine and scopolamine also put patients into a state of semiconsciousness in which operations can be performed; but on the whole, they are more dangerous than the inhalation anesthetics.

Other Uses of Chloroform and Ether.—Chloroform is an active irritant, used externally in rubefacient liniments, and in small doses internally in colic. Ether, internally, acts as a diffusible stimulant and carminative, being taken as spirits of ether or Hoffmann's anodyne.

HYPNOTICS OR SOMNIFACIENTS

There are many analogies between sleep and general anesthesia, sleep being a kind of physiological anesthesia.

Accordingly, the majority of the hypnotics belong to the same group as chloroform and ether. Examples of these aliphatic hypnotics are *chloral*, *paraldehyde*, *ethyl carbamate* (urethane), *sulphonmethanum* (sulphonal); *diethylbarbituric acid* (veronal), etc. Alcohol is also a hypnotic.

The chief difference between the anesthetics and these hypnotics is in the rapidity and duration of the action. The effects of the hypnotics must be slower and more prolonged. In practice, the dose of the hypnotic is usually adjusted so as to quiet the patient sufficiently to enable him to pass into a natural sleep, avoiding the larger doses which would actually produce a narcotic sleep. The use of hypnotics is very liable to create a habit and tolerance, so that ever increasing doses are required, which may become dangerous. This is one reason why the employment of hypnotic drugs should be avoided as much as possible, and the responsibility for their use intrusted to physicians.

Chloral.—This may be considered the type of the aliphatic hypnotics. It was the first to be discovered, and is still one of the strongest and most satisfactory. It was introduced by Liebreich, who believed that it would be transformed in the body into chloroform, as it is in the test-tubes by the action of alkalies. This does not occur, the chloral acting as such. Its action, however, is closely related to that of chloroform. Like this, large doses depress the heart and respiration, but the danger is not serious when small doses are used. Strong solutions also produce gastric irritation. In order to reduce the dosage chloral is often combined with other hypnotics, such as morphine or bromides. It must not be forgotten that these do not obviate the dangers of chloral in corresponding doses. The claims for proprietary mixtures of the bromidia type are thoroughly vicious.

Veronal (diethylbarbituric acid).—This is perhaps somewhat more efficient than chloral, and is a useful hypnotic. Large doses, however, have produced serious intoxication; and continued use of ordinary doses may produce chronic poisoning resembling sulphonal, although not as rapidly. The soluble sodium salt acts more promptly.

Sulphonal (Sulphonmethanum).—This acts with peculiar slowness, sleep occurring only after several hours; some depression extends into the next day. The drug is but slowly excreted, and therefore tends to produce cumulative effects, which may lead to very serious poisoning. Particularly characteristic is the appearance in the urine of *hematoporphyrin*, a peculiar derivative of hemoglobin. To guard against these dangers, sulphonal should not be used longer than a week at a time.

Paraldehyde.—This is rather weaker, but very prompt. Its chief drawbacks are the disagreeable odor and taste and some gastric irritation.

Ethyl Carbamate (**Urethane**).—This is almost too mild to be efficient.

Acute Poisoning by the Aliphatic Hypnotics.—The *symptoms* consist in profound coma, fall of temperature, and depressed heart and respiration. The *treatment* comprises washing of the stomach (emetics being often ineffective); caffeine, heat and artificial respiration when necessary.

Alcohol.—This may be considered among the hypnotics, although it is not often prescribed for this purpose, since effective doses produce too many undesired actions.

These fall under two headings: acute and chronic effects. Habitual use of alcohol induces a limited tolerance of the acute effects; it at the same time leads to the development of slow, gradual changes which constitute the chronic effects.

Acute Actions.—These resemble those of the anesthetics, ether, etc., but occur more slowly. They may be divided into the stimulant and the narcotic manifestations.

Alcoholic Stimulation.—The first effects of moderate doses of alcohol are apparently stimulant; consisting in excitement, increased respiration, rapid pulse, and flushed skin. These effects are only in minor part due to direct stimulation, but in greater part to reflexes and to disturbance of the brain, unbalanced judgment, etc.

Narcotic Action.—With larger doses, the apparent stimulation is followed by marked incoördination, mental and muscular, stupor, coma and (rarely) death.

The details of these actions may be discussed with the uses of alcohol.

Local Uses.—Strong alcohol coagulates protoplasm by abstracting water, and therefore acts as an irritant, without destroying the tissues. The action is proportionate to the concentration. Alcohol (about 25 to 50 per cent.) is therefore employed as a rubefacient. Weaker solutions (about 15 per cent.) are applied to ulcers, etc. to promote healing. Concentrations about 70 per cent. are actively antiseptic, weaker or stronger solutions are less efficient.

Digestion.—Small doses, of concentrations below 20 per cent., may rather favor digestion (unless inflammation is present) by increasing the circulation of the digestive organs, stimulating peristalsis, hastening absorption and favoring somewhat the action of the ferments. Higher concentrations, especially when used continuously, produce a harmful irritation and gastritis.

Food-equivalent.—Something like 98 per cent. of alcohol is burned in the body to carbon dioxide and water, much as it is burned in a lamp. The energy liberated in this way can be utilized, as with any other non-nitrogenous food. Since alcohol does not require digestion,

it sometimes has advantages, for instance, in fevers. On the other hand, its side actions make it entirely unsuitable as an ordinary food. It must be remembered that alcohol, while it is a food, is also a poison.

Chills and Exposure.—Alcohol dilates the vessels of the skin and brings more blood to the surface. This gives the *sensation* of warmth. At the same time, it exposes a larger volume of blood to cooling, and therefore tends to *lower the temperature* of the body. Alcohol is therefore dangerous *during* exposure to cold. *After* the exposure, it is beneficial by restoring the circulation of the skin more rapidly. It is likewise useful in fevers as an antipyretic, as well as a food.

Personal Efficiency.—An individual under alcohol feels himself more efficient, mentally and physically, but this sensation is mainly illusory. Exact observation shows that a real increase in efficiency is very slight and brief; and that the net result is depression. However, the mere feeling of capability may act as a tonic in depressed states, for instance, in convalescence.

Collapse.—The reflex stimulation produced by alcohol is useful in brief conditions of collapse, temporary heart failure, etc. In persistent collapse alcohol would be harmful through its direct depressant action on the nerve centers.

Treatment of Acute Alcoholic Poisoning.—The first indication is to empty the stomach. Apomorphine may be employed, since it also has a sedative and hypnotic effect in this condition. In mild cases, caffeine may suffice. It stimulates the centers which alcohol depresses.

Chronic Alcoholism.—The persistent use of alcohol induces a habituation, with mental and physical degenerations. The former are too well known to require description. The physical effects start with irritation

of the digestive tract—gastritis; then the liver is involved, with overgrowth of connective tissue (cirrhosis). The blood-vessels also show changes. Those of the skin become congested, and the larger vessels become hardened (arteriosclerosis). Gout and nephritis are other common results of alcoholism.

Treatment of Chronic Alcoholism.—This consists in withdrawing the drug and instituting tonic measures. So-called "cures" are mostly fraudulent.

Methyl Alcohol (Wood Alcohol, Columbian Spirits).—The acute effects are similar to those of ordinary alcohol, but more severe and toxic. However, these acute effects are often followed by incurable *blindness.* This may result also from the external application or even from inhalation of the vapors. Methyl alcohol must therefore never be used in medicine; and even its technical use must be carefully guarded.

Congeners, Fusel Oil, Amyl Alcohol, etc.—These form the special flavor, good or bad, of the ordinary liquors. They are popularly supposed to modify the effects of the alcohol, favorably or unfavorably, but little is known scientifically about their actions.

Morphine.—This is sometimes used as a hypnotic, especially if the loss of sleep is due to pain. Ordinary doses have little effect in other forms of insomnia, such as nervousness; and effective doses present grave danger of habit-formation. The use of morphine as a somnifacient should therefore be confined to acute painful conditions, as after operations; and in hopeless cases.

We may review in this place the other important data on morphine, many of which have been mentioned in other connections. What is said of morphine applies equally to opium.

Effects.—Increasing doses of morphine produce successively: Drowsiness, sleep and coma, with depression

of the respiration, and but little effect on the circulation. These effects are due to depression of the central nervous system, especially of the brain. The reflexes, which have their seat in the spinal cord, are not depressed; nor has it practically any action on the peripheral nerves, so that the local use of morphine as an analgesic is irrational: if its local application has any effect, this is due to the absorption of the drug.

Therapeutic Uses.—Morphine is used especially in the following conditions:

Cough.—Very small doses suffice to depress the response of the respiratory center to the reflex irritations which ordinarily evoke cough. The effect is purely symptomatic—the bronchitis which causes the cough is not cured; but the symptomatic relief is often important, especially if the cough interferes with sleep. Codeine and heroine are equally effective. Codeine is advocated as being much less liable to create a habit; whilst heroine deserves condemnation.

Diarrhea.—Morphine and opium arrest diarrhea by a local action, relatively small doses being effective. This also is a symptomatic treatment, since the cause of the diarrhea is not removed. Opiates should therefore not be used until the intestines have been thoroughly cleansed by castor oil, etc. Opium is rather more effective.

Pain.—Morphine is the most efficient of all drugs against all kinds of pain; but its use should be avoided in any but the most acute conditions, for fear of habit.

Hypnotic.—We have just considered its limtiations.

Idiosyncrasies.—In some individuals, morphine, instead of quieting, produces excitement. More common are the occurrence of nausea and vomiting. Sometimes it causes a disagreeable itching, especially of the nose.

Acute Morphine- and Opium-poisoning.—This is characterized by narcosis, starting with drowsiness, and ending in complete coma. The pin-point pupils help to distinguish morphine coma from other comas; but at death the pupils may again dilate.

The *treatment* consists in potassium permanganate to oxidize the unabsorbed morphine. The stomach should be washed out, even if the drug has been administered hypodermically since it is excreted into the stomach. Emetics would be unreliable in deep narcosis. Caffeine may be given to combat the depression, and the patient kept awake by walking; or revived if necessary by counterirritants. Artificial respiration may be necessary.

Chronic poisoning by opium and morphine and heroine are unfortunately too well known.

Repeated doses—and in some susceptible individuals a single administration—of these alkaloids leads to the production of persistent drug habits, which result in almost irresistible craving and inordinate tolerance of these drugs; and to physical, mental and moral degenerations which are very difficult to cure.

These symptoms set in so gradually that it may be impossible to discover them for a time; but the more advanced cases, with constricted pupils, emaciated and sallow cachectic skin, and especially the hypodermic marks, make detection easier.

The patient's will power is so weakened that it is almost impossible to break the habit by himself; and if the drug is withdrawn, there are violent and sometimes dangerous *abstinence symptoms*—cramps in the abdomen and muscles; digestive disturbances and collapse. The withdrawal must therefore be practiced cautiously, the patient being meanwhile supported by drugs. Scopolamine has been especially successful. Such treatment must be carried out in institutions, where the patient can

be carefully watched. The cured patients often relapse at some future time.

The best treatment is prevention. These drugs should be avoided in chronic conditions, and especially in patients with a nervous temperament. The sale of habit-forming drugs should be altogether prohibited except on a physician's prescription, thus forcing the habitués to seek treatment and making it impossible for them to relapse.

Apomorphine.—Although this is used mainly as an emetic, small doses are said to act also as a hypnotic under certain conditions, especially in alcoholic excitement. The dose is 1/40 grain—just about nauseant.

Lactucarium, Lupulin and Hops.—These are popularly credited with sedative and somnifacient qualities; but their actions—if they possess any—are so weak as to be totally unreliable. They have been practically discarded.

Cannabis.—The tops and resin of the hemp plant are used in various forms, in the Orient, as intoxicants and narcotics. In susceptible individuals, active preparations produce excitement, confusion, delirium and sleep. The activity, however, is very uncertain; and the preliminary excitement would render cannabis a poor hypnotic. It is often added to headache remedies but it is of doubtful value.

The uncertainty lies partly in the susceptibility of the patients, partly in the variability of the preparations. The activity is due to a resinous oil, which is easily destroyed by oxidation on keeping. It was claimed that only the Oriental hemp is active; but it is now recognized that American hemp has the same properties, though it is generally weaker. The addition of cannabis to corn-remedies can only serve for coloring.

The U.S.P. requires the bio-assay of cannabis on dogs.

These respond to appropriate doses by incoördination (clumsy walking).

Mineral Hypnotics—Bromides.—The only inorganic hypnotics are the bromides. All bromides and hydrobromic acid act alike; fairly large doses producing a slow depression of the excitability of the central nervous system. In man, 1 to 3 Gm. exert a mild hypnotic action, suited especially to "nervousness." They are also useful as adjuvants to other more powerful hypnotics—chloral, morphine, etc.—which may thus be used in smaller doses.

Larger doses of the bromides depress the reflexes, so that, for instance, the pharynx may be touched after gagging. These full doses are employed in the most common type of epilepsy. To be effective, high doses must be employed, requiring the supervision of a physician. These prevent the attacks, to a certain degree, but they do not usually cure the disease, so that the attacks recur when the drug is discontinued. However, they are vastly more effective than the other remedies that have been tried, such as zinc oxide, silver, solanum, belladonna, etc. These are all without effect.

The various bromides—K, Na, NH_4, Sr, Ca, Zn, etc., all act essentially alike. The sodium salt is probably the best; potassium is more irritant; ammonium tastes much worse; strontium and calcium are perhaps absorbed more slowly. There is no advantage in combining the various bromides, although this is often done.

Side Effects.—Bromides often give rise to irritant effects entirely analogous to iodism: acne and other skin eruptions, coryza, digestive derangements, etc. Further, their continued use is apt to result in mental dulness and melancholia. All these side actions cede rapidly on the withdrawal of the drug.

DELIRIFACIENTS

This term is applied to drugs which produce delirium and excitement. Most of these have already been discussed, viz. cannabis, opium, cocaine and atropine. The latter, however, requires some further discussion.

Atropine Group.—This comprises a number of plants of the potato family (Solanaceæ); especially belladonna, stramonium, scopola, and hyoscyamus. These all have similar active constituents, viz., a series of alkaloids, of which atropine, hyoscyamine and scopolamine are the most important. Since these produce mydriasis (dilation of the pupils), they are often called the "mydriatic alkaloids." Scopolamine is relatively abundant in hyoscyamus, so that this drug corresponds in its actions more nearly to this alkaloid; while the other drugs resemble atropine.

Actions of Atropine.—Moderate doses of atropine stimulate the central nervous system; large doses produce general paralysis. The most important effects, however, consist in peripheral paralysis of the nerves of involuntary muscles and of glands, namely:

Eye.—Atropine paralyzes the endings of the nerve (oculomotor) which constricts the pupils. The pupil is therefore dilated. This action is used extensively in eye-practice, for instance, in fitting glasses. The effect lasts several days, and is very disturbing to vision; so that the more rapidly acting derivative *homatropine* is often preferred. They may also provoke an attack of a serious eye-disease, glaucoma, in pre-disposed patients.

Heart.—The rate is quickened by paralysis of the vagus endings.

Bronchi.—These are relaxed through paralysis of their nerves. This is utilized in treatment of asthma, which

consists in spasmodic contraction of the bronchial muscles. In a similar manner, it paralyzes the muscles of the bile-ducts and ureters, and is therefore used in *biliary and renal colic.*

Intestines.—The effects of atropine on peristalsis are quite complex, varying with conditions. It is used to mitigate intestinal spasm, for instance, in lead-poisoning; and to regulate the griping action of purgatives.

Secretions.—Practically all secretions, except bile, milk and urine, are suppressed by atropine. It is used especially against excessive sweating and in coryza, etc.

Sensory Nerves.—These are somewhat depressed on local contact. This is utilized in the form of belladonna liniment, etc., in neuralgias and similar pains.

Central Action.—These are used particularly to stimulate the respiration, and in morphine-poisoning.

Symptoms of Atropine-poisoning.—These are very characteristic, but run a slow course. The *peripheral effects* occur first: dilated pupils; dry mouth and skin; difficult swallowing; headache; fast heart; flushing of the skin, which has been mistaken for scarlet fever.

The *central effects* consist in excitement and delirium. This may last for several days, and has been mistaken for insanity. Death occurs late, and the fatality is relatively small, so that there is a good chance for treatment.

Treatment.—This consists in evacuation, with the usual chemical alkaloidal antidotes; bromides; and artificial respiration in the later stages, if necessary.

Scopolamine and Hyoscine.—These are synonyms for the same alkaloid. If pure, these are identical whether prepared from scopola or hyoscyamus, and the impure are not constant. In fact, the commercial samples, whatever their origin, generally consist of mixtures of two isomeric alkaloids, differing in their behavior to polarized light; one being optically inactive, the other

levo-rotary. Both produce the specifically desirable central actions to the same degree, but levo-scopolamine (which is the one official in the U.S.P.) has more pronounced peripheral actions, resembling those of atropine.

Central Actions.—Scopolamine is a hypnotic, analgesic and sedative in certain conditions; in others it is of little effect. It is employed particularly in delirium and in insanity; and it strengthens the effects of morphine, for instance, in preparation for anesthesia. This has come into prominence through its use in childbirth—a rather dangerous procedure.

TABULATION OF AVERAGE DOSES

The following list may aid in memorizing the subject. The drugs have been divided into four groups, according to the order of their practical importance.

AVERAGE DOSES

GROUP A.—HIGHEST IMPORTANCE

Drug	Dose	Drug	Dose
Scopolamine	0.0003	Acetanil	0.2
Atropine	0.0005	Hexam	0.25
Strophanthin	0.001	Acetphen	0.3
Strychnine salts	0.0015	Iodides, sod., pot., etc	0.3
Arsen. triox	0.002	Bismuth, insol. salts	0.5
Mercuric salts	0.003	Chloral hydr	0.5
Apomorph, hydrochl	0.005	Tr. digit	0.5
Morphine salts	0.008	Tr. opii	0.5
Pilocarpine salts	0.01	Bicarb., sod. or pot	1
Hydrarg. chlor. mit	0.015	Bromides, sod., pot., etc	1
Codeine salts	0.03	Salicylates, sod. or stront	1
Sp. glyceryl. nit	0.05	Inf. digit	4
Opium	0.06	Tr. opii camph	4
Quinine salts	0.1		
Arsenic solutions	0.2		
(Except liq. arsen. et hg. iod.	0.1)		

GROUP B.—VERY IMPORTANT

Drug	Dose	Drug	Dose
Phosphor	0.0005	Aloe	0.25
Epineph	0.0005	Cupr. sulph	0.25
Physostigmine, sal	0.001	Ferr. carb. sacch	0.25
Diacetylmorph hydrochl	0.003	Mass. ferr. carb	0.25
Elaterine	0.003	Mass. hydrarg	0.25
Antim, et pot. tart	0.005	Terpin hydr	0.25
Res. podolph	0.01	Acid acetyl sal	0.3
Aloin	0.015	Ammon. carb. or chlor	0.3
Ol. tiglii	0.05	Ergot, fldext	2
Digit	0.06	Mag. oxide	2
Santonin	0.06	Oleores. aspid	2
Sod. cacodyl	0.06	Paraldehyde	2
Sod. nitris	0.06	Pulv. jalap. co	2
Caffeine	0.15	Sp. ammon. arom	2
Amyl nitris	0.2	Mag. carb	3
Camph	0.2	Pulv. glycyrrh. Co	4

Group B.—Very Important—(*Continued*)

Drug	Dose
Antipyr	0.3
Caff. cit. or caff. sod. benz	0.3
Tr. aconit	0.3
Ol. santal	0.5
Pulv. ipecac. et opii	0.5
Salvarsan	0.5
Tr. nuc. vom	0.5
Tr. strophanth	0.5
Veronal	0.5
Methyl salicyl	0.75
Neosalvarsan	0.75
Sulphonal or trional	0.75
Acetate, pot. or sod	1
Acid. hydrochl. dil	1
Calc. carb	1
Casc. sagr. fldext	1
Citrate, pot. or sod	1
Ipecac	1
Liq. hypophysis	1
Syr. ipecac	1
Syr. ferr. iod	1
Theobrom. sodio-sal	1
Zinc. sulph	1
Casc. sagr. arom. fldext	2
Sod. phos	4
Ol. morrh	10
Pot. et sod. tart	10
Syr. rhei arom	10
Ol. ricin	15
Petrolat. liq	15
Sulphate, mag. or sod	15
Liq. mag. cit	300

Group C.—Fairly Important

Drug	Dose
Aconitine	0.00015
Hyoscyamine	0.0003
Colchicine	0.0005
Homatrop. hydrobr	0.0005
Ouabain	0.0005
Hydrarg. salic	0.004
Sod. arsen	0.005
Arg. nit	0.01
Ext. cannab	0.01
Hydrarg. iod. flav	0.01
Hydrastine	0.01
Sparteine sulph	0.01
Ethylmorph. hydrochl	0.015
Ext. bellad. fol	0.015
Cocaine hydrochl	0.015
Emetine hydrochl	0.02
Erythr. tetranit	0.03
Ext. opii	0.03
Hydrastinin hydrochl	0.03
Bellad. rad., fldext	0.05
Cannab., fldext	0.05
Fldext. ipecac	0.05
Ol. phosphor	0.05
Papaverine sulph	0.05
Thiosinamine	0.05
Cotarnine hydrochl	0.06
Ext. colch	0.06
Ext. hyoscy	0.06
Ferr. reduct	0.06
Phenol	0.06
Plumb, acet	0.06
Pot. permang	0.06
Acid. hydrocyan. dil	0.1
Ext. fel. bov	0.1
Ferr. sulph. exsic	0.1
Tr. iodi	0.1
Resorcin	0.125
Thymol	0.125
Zinc. acet. or valer	0.125
Cinchonin. or cinchonidin. sulph.	0.15
Methylthionin. chlor	0.15
Phenolphthal	0.15
Volatile oils	0.2
(Except ol. amygd. amar	0.03)
(Except ol. tereb. rect	0.3)
(Except ol. cubeb	0.5)
(Except ol. eucalypt	0.5)
(Except ol. santal	0.5)
(Except ol. gaulth	0.75)
Benzosulphinide (sod.)	0.2
Bromoform	0.2
Hyoscy., fldext	0.2
Liq. iodi co	0.2
Ol. chenopod	0.2
Quin. tann	0.2
Asafet	0.25
Creosot	0.25
Ext. casc. sagr	0.25
Ext. ergot	0.25
Ext. gent	0.25
Ext. rhei	0.25
Ferr. et ammon. cit	0.25
Ferr. phos	0.25
Glycerophos., calc. or sod	0.25

GROUP C.—FAIRLY IMPORTANT—(*Continued*)

Hydrarg. c. cret	0.25
Iodof	0.25
Pellet. tann	0.25
Pot. chloras	0.25
Sod. phenolsulph	0.25
Tereben	0.25
Theophyllin	0.25
Tr. gelsem	0.25
Chlorof	0.3
Phenyl sal	0.3
Piperazin	0.3
Acid. benz	0.5
Acid. bor	0.5
Acid phenylcinch	0.5
Acid. tann	0.5
Alum	0.5
Butyl chloral hydr	0.5
Calc. chlor. or lact	0.5
Chlorbutanol	0.5
Guaiacol	0.5
Hypophos. calc. or pot	0.5
Lith. carb. and citr	0.5
Oleores. cubeb	0.5
Pancreat	0.5
Pepsin	0.5
Pot. nitras	0.5
Tr. cannabis	0.5
Tr. capsic	0.5
Tr. ferr. chlor	0.5
Tr. veratr. vir	0.5
Apocyn. fldext	0.75
Sod. bor	0.75
Tr. bellad. fol	0.75
Acid. camph	1
Acid. nitrohydrochl. dil	1
Ether	1
Ethyl carbam	1
Benzoates, sod. or ammon	1
Carbo lig	1
Copaib	1
Ext. tarax	1
Guaiacol. carb	1
Quin. et ureae hydrochl	1
Salicin	1
Sp. camph	1
Sod. hypophos	1
Tannalbin	1
Tr. lobel	1
Tr. scill	1
Vin. antim	1
Vin. colch	1
Sod. phos. acid	1.5
Spirits	2
(Except sp. glyceryl nit	0.05)
(Except sp. amygd. amar	0.5)
(Except sp. aether	4)
(Except sp. juniper co	10)
Acid. acet. dil	2
Acid. phosp. dil	2
Acid. sulph. arom	2
Fldext. buchu	2
Fldext. glycyrrh	2
Fldext. senn	2
Fldext. hydrast	2
Pot. bitart	2
Sp. aether. nitros	2
Sp. chlorof	2
Syr. scill	2
Syr. scill. co	2
Tr. card	2
Tr. colch	2
Tr. guaiac ammon	2
Tr. hyoscy	2
Tr. quass	2
Tr. rhei arom	2
Tr. valer. ammon	2
Tr. zingib	2
Uvae ursi, fldext	2
El. ferr. quin. et strych. phos	4
Glycerine	4
Liq. hydrog. dioxide	4
Magma bism	4
Pot. cit. eff	4
Senn	4
Sp. aether	4
Sulphur	4
Syr. pic. liq	4
Syr. seneg	4
Syr. senn	4
Tr. calumb	4
Tr. card. co	4
Tr. cinch. and co	4
Tr. gambir Co	4
Tr. gent. co	4
Tr. hydrast	4
Tr. kino	4
Agar	10
Aq. camph	10
Aq. creosot	10
Magma mag	10
Mist. glycyrrh. co	10
Sinapis	10

Group C.—Fairly Important—(*Continued*)

Syr. hypophos	10
Flavoring syrups	15
(Except pic. liq	4)
(Except pruni. virg	4)
Flavoring waters	15
(Except aq. amygd. amar	4)
Aq. chlorof	15
Emuls. asafoet	15
Emuls. ol. morrh	15
Ext. malt	15
Liq. ammon. acet	15
Liq. calc	15
Mist. cret	15
Mucil. acac	15
Ol. oliv	30
Ferr. hydrox. c. magn. oxide	120

Group D.—Slight Importance

Arsen. iod	0.005
Aur. et sod. chlor	0.005
Iodum	0.005
Sod. arsen. exsic	0.005
Ext. physostig	0.008
Ext. aconit	0.01
Ext. gelsem	0.01
Ext. stramon	0.01
Ferr. sulph	0.01
Hydrarg. succinim	0.01
Uran. nit	0.01
Aconit. fldext	0.03
Benzaldehyde	0.03
Chrysarobin	0.03
Ext. colocynth	0.03
Gelsem. fldext	0.03
Hypophysis sicc	0.03
Oleores. capsic	0.03
Oleores. piper	0.03
Oleores. zingib	0.03
Trinitrophen	0.03
Trit. elaterin	0.03
Vanillin	0.03
Cresol	0.05
Menthol	0.05
Liq. ferr. subsulph	0.2
Ol. pic. liq	0.2
Res. scammon	0.2
Betanapthol	0.25
Caryoph	0.25
Ext. cimicif	0.25
Cinnam	0.25
Colch. corm	0.25
Ext. colocynth. co	0.25
Ext. sumbul	0.25
Ferr. et quin. cit	0.25
Glycrrh. ammon	0.25
Mangan. diox. praec	0.25
Mosch	0.25
Scammon. rad	0.25
Sod. carb. moohyden	0.25
Suprarен. sicc	0.25
Zinc. oxide	0.25
Eucalyptol	0.3
Glycer. phenol	0.3
Liq. sod. glycerophos	0.35
Acid. hydriod. dil	0.5
Acid. hypophos. dil	0.5
Acid. tart	0.5
Ammon. salicyl	0.5
Anis	0.5
Coriand	0.5
Diastas	0.5
Euonym. cort	0.5
Ext. hydrast	0.5
Ext. viburn. prunif	0.5
Galla	0.5
Kino	0.5
Lupulin	0.5
Myrist	0.5
Myrrh	0.5
Oleores. petrosel	0.5
Ol. cajup	0.5
Ol. cubeb	0.5
Ol. eucalypt	0.5
Piper	0.5
Pix. liq	0.5
Podoph., fldext	0.5
Quass	0.5
Tr. stramon	0.5
Acid. salicyl	0.75
Acet. scill	1
Acids, dilute: hydrobr., nitr., sulph	1
Acid. gall	1
Amylen hydr	1
Aq. ammon	1
Benzoin	1
Card. sem	1
Carum	1

Group D.—Slight Importance—(*Continued*)

Chloral formam	1
Cimicif., fledxt	1
Cinch., fledxt	1
Cresot. carb	1
Cubeb	1
Fldext. arom	1
Fldext. erodict	1
Fldext. sabal	1
Foenic	1
Frangul., fldext	1
Gambir	1
Manna	15
Matricar	15
Liq. ferr. et ammon. acet	15
Liq. pot. cit	15
Nuc. vom. fldext	0.05
Sod. arsanil	0.05
Arg. oxide	0.06
Bellad. fol	0.06
Calc. sulph. ven	0.06
Capsic	0.06
Colocynth	0.06
Euonym. ext	0.06
Ferr. chlor	0.06
Staphisag	0.06
Stramon	0.06
Strophanthus	0.06
Tr. canthar	0.1
Liq. ferr. chlor	0.1
Scill. fldext	0.1
Verat. vir. fldext	0.1
Bism. et. ammon. cit	0.125
Cambog	0.125
Camph. monobrom	0.125
Lobel. fldext	0.125
Res. jalap	0.125
Sanguin	0.125
Zinc phenolsulph	0.125
Colch. sem. fldext	0.2
Eugenol	0.2
Gentian fldext	1
Guaiac	1
Ichthyol	1
Jalap	1
Lactucar	1
Liq. ferr. dial	1
Liq. potass. or sod. hydrox	1
Pot. carb	1
Pulv. arom	1
Rhei, fldext	1
Seneg	1
Serpent	1
Sod. sulphis exsic	1
Sod. thiosulph	1
Styrax	1
Tr. arnic	1
Tr. asafoet	1
Tr. benzoin	1
Tr. myrrh	1
Tr. physostig	1
Vin. ipecac	1
Zingib., fldext	1
Calumb	2
Emul. ol. tereb	2
Eucalypt., fldext	2
Granat., fldext	2
Gossyp. rad. cort. fldext	2
Grindel., fldext	2
Guaran., fldext	2
Pareira	2
Pilocarp., fldext	2
Prun. virg	2
Pulv. cret. co	2
Pulv. rhei co	2
Pyreth	2
Sarsap., fldext. and co	2
Sumbul., fldext	2
Sod. phos. exsic	2
Stilling. fldext	2
Tr. aloes	2
Tr. benzoin co	2
Tr. cinnamon	2
Tr. lactucar	2
Tr. lavand	2
Tr. tolut	2
Valer	2
Viburn. prunif., fldext	2
Xanthox., fldext	2
Aspide	4
Aspidosp., fldext	4
Mel rosae	4
Menth., pip. or vir	4
Spigel, fldext	4
Syr. acid. hydriod	4
Tr. guaiac	4
Tr. mosch	4
Tr. rhei	4
Tr. valer	4
Liq. sod. phos	10
Sassafras	10
Sod. phos. eff	10
Syr. calc. lactophos	10

Group D.—Slight Importance—(*Continued*)

Syr. lactucar	10	Sod. chlor	15
Syr. rhei	10	Ol. lini	30
Tarax. fldext	10	Pepo	30
Trit., fldext	10	Inf. senn. co	120

INDEX

SAUNDERS' BOOKS on

GYNECOLOGY

and

OBSTETRICS

W. B. SAUNDERS COMPANY

West Washington Square **Philadelphia**

0, Henrietta Street **Covent Garden, London**

Our Handsome Complete Catalogue will be Sent on Request

Graves' Gynecology

Text-Book of Gynecology. By WILLIAM P. GRAVES, M. D., Professor of Gynecology at Harvard Medical School. Large octavo of 770 pages, with 425 original illustrations, many in colors. Cloth, $7.00 net; Half Morocco, $8.50 net.

JUST ISSUED

This new work presents gynecology along new lines. An entire section is devoted exclusively to the *physiology* of the pelvic organs and to *correlated gynecology*—the relationship of gynecology to organs of *internal secretion*, breast, skin, organs of sense, digestion and respiration, blood, circulatory apparatus, abdominal organs, nervous system, bones, and joints. A special section is devoted to *enteroptosis*, intestinal bands, and movable kidney.

The second portion of the book is devoted to special gynecologic disease and is arranged particularly for the convenience of medical students. The first two parts (covering 500 pages) are entirely *non-surgical*, giving only drug and mechanical therapy and material invaluable to the general practitioner. The third part is exclusively a treatise on *surgical gynecology*, and includes profusely illustrated descriptions of those gynecologic operations that to the author seem most feasible. A number of new operations are given and illustrated.

DeLee's New Obstetrics

Text-Book of Obstetrics. By JOSEPH B. DELEE, M. D., Professor of Obstetrics at Northwestern University Medical School, Chicago. Large octavo of 1087 pages, with 938 illustrations, 175 in colors. Cloth, $8.00 net; Half Morocco, $9.50 net.

NEW (2d) EDITION

You will pronounce this new book the most elaborate, the most superbly illustrated work on Obstetrics you have ever seen. Especially will you value the 938 illustrations, all, with but few exceptions, original, and the best work of leading medical artists. Some 175 of these illustrations are in color. **Such a magnificent collection of obstetric pictures—and with *really practical value*—has never before appeared in one book.**

You will find the text extremely practical throughout. *Diagnosis* is featured, and the relations of obstetric conditions and accidents to general medicine, surgery, and the specialties are brought into prominence.

Regarding *Treatment:* You get here the very latest advances in this field, and you can rest assured every method of treatment, every step in operative technic, is just right. Dr. DeLee's twenty-one years' experience as a teacher and obstetrician guarantees this.

Worthy of your particular attention are the descriptive legends under the illustrations. These are unusually full, and by studying the pictures serially with their detailed legends you are better able to follow the operations than by referring to the pictures from a distant text—the usual method.

Prof. W. Stoeckel, *Kiel, Germany*

"Dr. DeLee's Obstetrics deserves the greatest recognition. The whole work is of such sterling character through and through that it must be ranked with the best works of our literature."

Norris' Gonorrhea in Women

GONORRHEA IN WOMEN. By CHARLES C. NORRIS, M. D., Instructor in Gynecology, University of Pennsylvania. With an Introduction by JOHN G. CLARK, M. D., Professor of Gynecology, University of Pennsylvania. Large octavo of 520 pages, illustrated. Cloth, $6.00 net; Half Morocco, $7.50 net.

Davis' Manual of Obstetrics

Manual of Obstetrics. By EDWARD P. DAVIS, M. D., Professor of Obstetrics in Jefferson Medical College. 12mo of 463 pages, with 171 original illustrations. Cloth, $2.25 net.

ORIGINAL ILLUSTRATIONS

Dr. Davis' manual is a concise text-book of exceptional value. Dr. Davis, himself a teacher of many years' experience, knows the requirements of such a work and has here supplied them. You get anatomy of the normal and abnormal bony pelvis, physiology of impregnation, anatomy of the birth canal in pregnancy, growth and development of the embryo. You get a full and clear discussion of pregnancy—its diagnosis, physiology, hygiene, pathology. You get the causes and treatment of labor, the physiology, conduct, pathology; the puerperal period—care of the mother and child; obstetric surgery, fetal pathology, mixed feeding, and medicolegal aspects of obstetric practice.

Davis' Operative Obstetrics

Operative Obstetrics. By EDWARD P. DAVIS, M. D., Professor of Obstetrics at Jefferson Medical College, Philadelphia. Octavo of 483 pages, with 264 illustrations. Cloth, $5.50 net; Half Morocco, $7.00 net.

INCLUDING SURGERY OF NEWBORN

Dr. Davis' new work on Operative Obstetrics is a most practical one, and no expense has been spared to make it the handsomest work on the subject as well. Every step in every operation is described minutely, and the technic shown by beautiful new illustrations. The section given over to surgery of the newborn you will find unusually valuable. It gives you much information you want to know—facts you can use in your work every day. There is an excellent chapter on anesthesia in obstetrics.

The Lancet, *London*

"The best and most interesting part of the book is the ***summary of results*** given at the end of the chapters and compiled from the author's own experience and from the literature."

Ashton's Practice of Gynecology

The Practice of Gynecology. By W. EASTERLY ASHTON, M. D., LL.D., Professor of Gynecology, University of Pennsylvania. Octavo of 1097 pages, containing 1052 original line-drawings. Cloth, $6.50 net; Half Morocco, $8.00 net

THE NEW (6th) EDITION

Among the important new matter may be mentioned the De Keating-Hart fulguration treatment, Coley's mixed toxins for sarcoma of the genito-urinary organs, the cutireaction of von Pirquet in the diagnosis of tuberculosis, "606" for syphilis, the hormone theory, the Fowler-Murphy treatment of suppurative peritonitis, tincture of iodin in sterilization, and Baldy's new round ligament operation for retrodisplacement. Nothing is left to be taken for granted, the author not only telling his readers in every instance what should be done, but also precisely *how to do it*. A distinctly original feature of the book is the illustrations, numbering 1058 line drawings made especially under the author's personal supervision.

From its first appearance Dr. Ashton's book set a standard in *practical* medical books; that he *has* produced a work of unusual value to the medical practitioner is shown by the demand for new editions.

Howard A. Kelly, M. D.,

Professor of Gynecologic Surgery, Johns Hopkins University

"It is different from anything that has as yet appeared. The illustrations are particularly clear and satisfactory. One specially good feature is the pains with which you describe so many *details* so often left to the imagination."

Charles B. Penrose, M. D.,

Formerly Professor of Gynecology, University of Pennsylvania.

"I know of no book that goes so thoroughly and satisfactorily into all the *details* of everything connected with the subject. In this respect your book differs from the others."

George M. Edebohls, M.D.

Professor of Diseases of Women, New York Post-Graduate Medical School.

"I have looked it through and must congratulate you upon having produced a textbook most admirably adapted to *teach* gynecology to those who must get their knowledge, even to the minutest and most elementary details, from books."

Bandler's Medical Gynecology

Medical Gynecology. By S. WYLLIS BANDLER, M. D., Adjunct Professor of Diseases of Women, New York Post-Graduate Medical School and Hospital. Octavo of 790 pages, with 150 original illustrations. Cloth, $5.00 net; Half Morocco, $6.50 net.

NEW (3d) EDITION—60 PAGES ON INTERNAL SECRETIONS

This new work by Dr. Bandler is just the book that the physician engaged in general practice has long needed. It is truly *the practitioner's gynecology*—planned for him, written for him, and illustrated for him. There are many gynecologic conditions that do not call for operative treatment; yet, because of lack of that special knowledge required for their diagnosis and treatment, the general practitioner has been unable to treat them intelligently. This work gives just the information the practitioner needs.

American Journal of Obstetrics

"He has shown good judgment in the selection of his data. He has placed most emphasis on diagnostic and therapeutic aspects. He has presented his facts in a manner to be readily grasped by the general practitioner."

Bandler's Vaginal Celiotomy

Vaginal Celiotomy. By S. WYLLIS BANDLER, M. D. Octavo of 450 pages, with 148 illustrations. Cloth, $5.00 net.

SUPERB ILLUSTRATIONS

The vaginal route, because of its simplicity, ease of execution, absence of shock, more certain results, and the opportunity for conservative measures, constitutes a field which should appeal to all surgeons, gynecologists, and obstetricians. Posterior vaginal celiotomy is of great importance in the removal of small tubal and ovarian tumors and cysts, and is an important step in the performance of vaginal myomectomy, hysterectomy, and hysteromyomectomy. Anterior vaginal celiotomy with thorough separation of the bladder is the only certain method of correcting cystocele.

The Lancet, London

"Dr. Bandler has done good service in writing this book, which gives a very clear description of all the operations which may be undertaken through the vagina. He makes out a strong case for these operations."

Hirst's Obstetrics

The New (7th) Edition

A Text-Book of Obstetrics. By BARTON COOKE HIRST, M. D., Professor of Obstetrics in the University of Pennsylvania. Handsome octavo, 1017 pages, with 895 illustrations, 53 in colors. Cloth, $5.00 net; Half Morocco, $6.50 net.

INCLUDING RELATED GYNECOLOGIC OPERATIONS

Immediately on its publication this work took its place as the leading text-book on the subject. Both in this country and abroad it is recognized as the most satisfactorily written and clearly illustrated work on obstetrics in the language. The illustrations form one of the features of the book. They are numerous and the most of them are original. In this edition the book has been thoroughly revised. Recognizing the inseparable relation between obstetrics and certain gynecologic conditions, the author has included all the gynecologic operations for complications and consequences of childbirth, together with a brief account of the diagnosis and treatment of all the pathologic phenomena peculiar to women.

British Medical Journal

"The illustrations in Dr. Hirst's volume are far more numerous and far better executed, and therefore more instructive, than those commonly found in the works of writers on obstetrics in our own country."

Hirst's Diseases of Women

A Text-Book of Diseases of Women. By BARTON COOKE HIRST, M. D. Octavo of 745 pages, 701 illustrations, many in colors. Cloth, $5.00 net; Half Morocco, $6.50 net.

SECOND EDITION

As diagnosis and treatment are of the greatest importance in considering diseases of women, particular attention has been devoted to these divisions. The palliative treatment, as well as the radical operation, is fully described, enabling the general practitioner to treat many of his own patients without referring them to a specialist.

Medical Record, New York

"Its merits can be appreciated only by a careful perusal. . . Nearly one hundred pages are devoted to technic, this chapter being in some respects superior to the descriptions in other text-books."

Kelly and Noble's Gynecology and Abdominal Surgery

Gynecology and Abdominal Surgery. Edited by HOWARD A. KELLY, M. D., Professor of Gynecology in Johns Hopkins University; and CHARLES P. NOBLE, M.D., formerly Clinical Professor of Gynecology in the Woman's Medical College, Philadelphia. Two imperial octavo volumes of 950 pages each, containing 880 illustrations, mostly original. Per volume: Cloth, $8.00 net; Half Morocco, $9.50 net.

BOTH VOLUMES NOW READY

WITH 880 ORIGINAL ILLUSTRATIONS BY HERMANN BECKER AND MAX BRÖDEL

In view of the intimate association of gynecology with abdominal surgery the editors have combined these two important subjects in one work. For this reason the work will be doubly valuable, for not only the gynecologist and general practitioner will find it an exhaustive treatise, but the surgeon also will find here the latest technic of the various abdominal operations. It possesses a number of valuable features not to be found in any other publication covering the same fields. It contains a chapter upon the bacteriology and one upon the pathology of gynecology, dealing fully with the scientific basis of gynecology. In no other work can this information, prepared by specialists, be found as separate chapters. There is a large chapter devoted entirely to *medical gynecology*, written especially for the physician engaged in general practice. Heretofore the general practitioner was compelled to search through an entire work in order to obtain the information desired. *Abdominal surgery* proper, as distinct from gynecology, is fully treated, embracing operations upon the stomach, upon the intestines, upon the liver and bile-ducts, upon the pancreas and spleen, upon the kidney, ureter, bladder, and the peritoneum. Special attention has been given to *modern technic*. The illustrations are the work of *Mr. Hermann Becker* and *Mr. Max Brödel.*

American Journal of the Medical Sciences

"It is needless to say that the work has been thoroughly done: the names of the authors and editors would guarantee this; but much may be said in praise of the method of presentation, and attention mav be called to the inclusion of matter not to be found elsewhere."

Webster's Diseases *of* Women

Diseases of Women. By J. CLARENCE WEBSTER, M. D. (EDIN.), F. R. C. P. E., Professor of Gynecology and Obstetrics in Rush Medical College. Octavo of 712 pages, with 372 illustrations. Cloth, $7.00 net; Half Morocco, $8.50 net.

FOR THE PRACTITIONER

Dr. Webster has written this work *especially for the general practitioner*, discussing the clinical features of the subject in their widest relations to general practice rather than from the standpoint of specialism. The magnificent illustrations, three hundred and seventy-two in number, are nearly all original. Drawn by expert anatomic artists under Dr. Webster's direct supervision, they portray the anatomy of the parts and the steps in the operations with rare clearness and exactness.

Howard A. Kelly, M.D., *Professor of Gynecologic Surgery, Johns Hopkins University.*

"It is undoubtedly one of the best works which has been put on the market within recent years, showing from start to finish Dr. Webster's well-known thoroughness. The illustrations are also of the highest order."

Webster's Obstetrics

A Text-Book of Obstetrics. By J. CLARENCE WEBSTER, M. D. (EDIN.), Professor of Obstetrics and Gynecology in Rush Medical College. Octavo of 767 pages, illustrated. Cloth, $5.00 net; Half Morocco, $6.50 net.

Medical Record, New York

"The author's remarks on asepsis and antisepsis are admirable, the chapter on eclampsia is full of good material, and . . . the book can be cordially recommended as a safe guide."

Kelly *and* Cullen's Myomata of the Uterus

Myomata of the Uterus. By HOWARD A. KELLY, M. D., Professor of Gynecologic Surgery at Johns Hopkins University; and THOMAS S. CULLEN, M. B., Associate in Gynecology at Johns Hopkins University. Large octavo of about 700 pages, with 388 original illustrations by August Horn and Hermann Becker. Cloth, $7.50 net; Half Morocco, $9.00 net.

A MASTER WORK

ILLUSTRATED BY AUGUST HORN AND HERMANN BECKER

This monumental work, the fruit of over ten years of untiring labors, will remain for many years the last word upon the subject. Written by those men who have brought, step by step, the operative treatment of uterine myoma to such perfection that the mortality is now less than one per cent., it stands out as the record of greatest achievement of recent times.

The illustrations have been made with wonderful accuracy in detail by Mr. August Horn and Mr. Hermann Becker, whose superb work is so well known that comment is unnecessary. For painstaking accuracy, for attention to every detail, and as an example of the practical results accruing from the association of the operating amphitheater with the pathologic laboratory, this work will stand as an enduring testimonial.

Surgery, Gynecology, and Obstetrics

"It must be considered as the most comprehensive work of the kind yet published. It will always be a mine of wealth to future students."

New York Medical Journal

"Within the covers of this monograph every form, size, variety, and complication of uterine fibroids is discussed. It is a splendid example of the rapid progress of American professional thought."

Bulletin Medical and Chirurgical Faculty of Maryland

"Few medical works in recent years have come to our notice so complete in detail, so well illustrated, so practical, and so far reaching in their teaching to general practitioner, specialist, and student alike."

Dorland's Modern Obstetrics

Modern Obstetrics: General and Operative. By W. A. NEWMAN DORLAND, A. M., M. D., Professor of Gynecology at the Post-graduate Medical School, Chicago. Octavo of 797 pages, with 201 illustrations. Cloth, $4.00 net.

Second Edition, Revised and Greatly Enlarged

In this edition the book has been entirely rewritten and very greatly enlarged. Among the new subjects introduced are the surgical treatment of puerperal sepsis, infant mortality, placental transmission of diseases, serum-therapy of puerperal sepsis, etc.

Journal of the American Medical Association

"This work deserves commendation, and that it has received what it deserves at the hands of the profession is attested by the fact that a second edition is called for within such a short time. Especially deserving of praise is the chapter on puerperal sepsis"

Davis' Obstetric and Gynecologic Nursing

Obstetric and Gynecologic Nursing. By EDWARD P. DAVIS, A. M., M. D., Professor of Obstetrics in the Jefferson Medical College and Philadelphia Polyclinic; Obstetrician and Gynecologist, Philadelphia Hospital. 12mo of 480 pages, illustrated. Buckram, $1.75 net.

NEW (4th) EDITION

This volume gives a very clear and accurate idea of the manner to meet the conditions arising during obstetric and gynecologic nursing. The third edition has been thoroughly revised.

The Lancet, London

"Not only nurses, but even newly qualified medical men, would learn a great deal by a perusal of this book. It is written in a clear and pleasant style, and is a work we can recommend."

Bandler's The Expectant Mother

THE EXPECTANT MOTHER. By SAMUEL WYLLIS BANDLER, M. D., Professor of Diseases of Women, New York Post-Graduate Medical School and Hospital. 12mo of 300 pages, illustrated. Cloth, $1.25 net.

Montgomery's Care of Gynecologic Cases

CARE OF PATIENTS: Before, During, and After Operation. By E. E. MONTGOMERY, M. D., LL.D., Professor of Gynecology in Jefferson Medical College. 12mo of 149 pages, illustrated.

Macfarlane's Gynecology for Nurses (2d) New Edition

A REFERENCE HAND-BOOK OF GYNECOLOGY FOR NURSES. By CATHARINE MACFARLANE, M. D., Gynecologist to the Woman's Hospital of Philadelphia. 16mo of 156 pages, with 70 illustrations. Flexible leather, $1.25 net.

A. M. Seabrook, M. D., *Woman's Medical College of Philadelphia.*

"It is a most admirable little book, covering in a concise but attractive way the subject from the nurse's standpoint."

American Text-Book of Gynecology Second Edition

AMERICAN TEXT-BOOK OF GYNECOLOGY. Edited by J. M. BALDY, M. D. Imperial octavo of 718 pages, with 341 text-illustrations and 38 plates. Cloth, $6.00 net.

American Text-Book of Obstetrics Second Edition

THE AMERICAN TEXT-BOOK OF OBSTETRICS. In two volumes. Edited by RICHARD C. NORRIS, M. D.; Art Editor, Robert L. Dickinson, M. D. Two octavos of about 600 pages each; nearly 900 illustrations, including 49 colored and half-tone plates. Per volume: Cloth, $3.50 net.

Matthew D. Mann, M. D.,

Professor of Obstetrics and Gynecology, University of Buffalo.

"I like it exceedingly and have recommended the first volume as a text-book. It is certainly a most excellent work. I know of none better."

Schäffer and Webster's Operative Gynecology

Atlas and Epitome of Operative Gynecology. By DR. O. SCHÄFFER, of Heidelberg. Edited, with additions, by J. CLARENCE WEBSTER, M. D. (EDIN.), F. R. C. P. E., Professor of Obstetrics and Gynecology in Rush Medical College, in affiliation with the University of Chicago. 42 colored lithographic plates, many text-cuts, a number in colors, and 138 pages of text. *In Saunders' Hand-Atlas Series.* Cloth, $3.00 net.

Much patient endeavor has been expended by the author, the artist, and the lithographer in the preparation of the plates for this Atlas. They are based on hundreds of photographs taken from nature, and illustrate most faithfully the various surgical situations. Dr. Schäffer has made a specialty of demonstrating by illustrations.

Medical Record, New York

"The volume should prove most helpful to students and others in grasping details usually to be acquired only in the amphitheater itself."

De Lee's Obstetrics for Nurses

Obstetrics for Nurses. By JOSEPH B. DE LEE, M. D., Professor of Obstetrics in the Northwestern University Medical School, Chicago; Lecturer in the Nurses' Training Schools of Mercy, Wesley, Provident, Cook County, and Chicago Lying-In Hospitals. 12mo of 508 pages, fully illustrated.

Cloth, $2.50 net.

NEW (4th) EDITION

While Dr. DeLee has written his work especially for nurses, the practitioner will also find it useful and instructive, since the duties of a nurse often devolve upon him in the early years of his practice. The illustrations are nearly all original and represent photographs taken from actual scenes. The text is the result of the author's many years' experience in lecturing to the nurses of five different training schools.

J. Clifton Edgar, M. D.,

Professor of Obstetrics and Clinical Midwifery, Cornell University, New York.

"It is far and away the best that has come to my notice, and I shall take great pleasure in recommending it to my nurses, and students as well"

Schäffer and Edgar's
Labor and Operative Obstetrics

Atlas and Epitome of Labor and Operative Obstetrics. By Dr. O. Schäffer, of Heidelberg. *From the Fifth Revised and Enlarged German Edition.* Edited, with additions, by J. Clifton Edgar, M. D., Professor of Obstetrics and Clinical Midwifery, Cornell University Medical School, New York. With 14 lithographic plates in colors, 139 other illustrations, and 111 pages of text. Cloth, $2.00 net. *In Saunders' Hand-Atlas Series.*

This book presents the act of parturition and the various obstetric operations in a series of easily understood illustrations, accompanied by a text treating the subject from a practical standpoint.

American Medicine

"The method of presenting obstetric operations is admirable. The drawings, representing original work, have the commendable merit of illustrating instead of confusing."

Schäffer and Edgar's
Obstetric Diagnosis and Treatment

Atlas and Epitome of Obstetric Diagnosis and Treatment. By Dr. O. Schäffer, of Heidelberg. *From the Second Revised German Edition.* Edited, with additions, by J. Clifton Edgar, M. D., Professor of Obstetrics and Clinical Midwifery, Cornell University Medical School, N. Y. With 122 colored figures on 56 plates, 38 text-cuts, and 315 pages of text. Cloth, $3.00 net. *In Saunders' Hand-Atlas Series.*

This book treats particularly of obstetric operations, and, besides the wealth of beautiful lithographic illustrations, contains an extensive text of great value. This text deals with the practical, clinical side of the subject.

New York Medical Journal

"The illustrations are admirably executed, as they are in all of these atlases, and the text can safely be commended, not only as elucidatory of the plates, but as expounding the scientific midwifery of to-day."

American Pocket Dictionary

New (9th) Edition

THE AMERICAN POCKET MEDICAL DICTIONARY. Edited by W. A. NEWMAN DORLAND, A. M., M.D. With 693 pages. Full leather, limp, with gold edges, $1.00 net; with patent thumb index, $1.25 net.

James W. Holland, M. D.,

Professor of Chemistry and Toxicology, at the Jefferson Medical College. Philadelphia.

"I am struck at once with admiration at the compact size and attractive exterior I can recommend it to our students without reserve."

Cragin's Gynecology

Eighth Edition

ESSENTIALS OF GYNECOLOGY. By EDWIN B. CRAGIN, M. D., Professor of Obstetrics, College of Physicians and Surgeons, New York. Crown octavo, 240 pages, 62 illustrations. Cloth, $1.00 net. *In Saunders' Question-Compend Series.*

Galbraith's Four Epochs of Woman's Life

Third Edition

THE FOUR EPOCHS OF WOMAN'S LIFE: A STUDY IN HYGIENE. Maidenhood, Marriage, Maternity, Menopause. By ANNA M. GALBRAITH, M. D. With an Introductory Note by JOHN H. MUSSER, M. D., University of Pennsylvania. 12mo of 247 pages.

Schaffer and Norris' Gynecology

Saunders' Atlases

ATLAS AND EPITOME OF GYNECOLOGY. By DR. O. SCHAFFER, of Heidelberg. Edited, with additions, by RICHARD C. NORRIS, A. M., M. D., Assistant Professor of Obstetrics, University of Pennsylvania. 207 colored illustrations on 90 plates, 65 text-cuts, and 272 pages of text. Cloth, $3.50 net.

Ashton's Obstetrics

Eighth Edition

ESSENTIALS OF OBSTETRICS. By W. EASTERLY ASHTON, M. D., Professor of Gynecology, University of Pennsylvania. Crown octavo, 290 pages, 125 illustrations. Cloth, $1.00 net. *In Saunders' Question-Compend Series.*

Southern Practitioner

"An excellent little volume, containing correct and practical knowledge. An admirable compend, and the best condensation we have seen."

Barton and Wells' Medical Thesaurus

A THESAURUS OF MEDICAL WORDS AND PHRASES. By WILFRED M. BARTON, M. D., Assistant to Professor of Materia Medica and Therapeutics, Georgetown University, Washington, D. C.; and WALTER A. WELLS, M. D., Demonstrator of Laryngology, Georgetown University, Washington, D. C. 12mo of 534 pages. Flexible leather, $2.50 net; with thumb index, $3.00 net.